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DOCUMENT-IDENTIFIER: US 5160737 A

TITLE: Liquid polymer composition, and method of use

DATE-ISSUED: November 3, 1992

INVENTOR-INFORMATION:

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PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S. application Ser. No. 07/432,667, abando filed Nov. 7, 1989, which is a continuation-in-part of U.S. patent application Ser. Nos. 07/189,918 (filed May, 3, 1988), abandoned, 07/304,091 (filed Jan. 31, 1989), 07/304,092 (filed Jan. 31, 1989), abandoned, and 07/369,223 (filed Jun. 21, 1989) abandoned, which applications are all incorporated herein by reference.

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FIELD-OF-SEARCH: 424/49, 424/54, 424/52, 424/401, 514/900, 514/901, 514/902

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	2984639	May 1961	Stamberger et al.	525/329.6
☐	3846542	November 1974	Gross	424/81
☐	3925895	December 1975	Kliment et al.	433/224
☐	3956480	May 1976	Dichter et al.	424/54
☐	4011309	March 1977	Lutz	424/49
☐	4539199	September 1985	Orban et al.	424/456
☐	4554156	November 1985	Fischer et al.	424/81
☐	4645662	February 1987	Nakashima et al.	424/52
☐	4683134	July 1987	Palinczar	424/59
☐	4701320	October 1987	Hasegawa et al.	424/54
☐	4751072	June 1988	Kim	424/49
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☐	4911922	March 1990	Matsuhara et al.	424/81
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Thoennes et al., Drug Dev. Indus. Pharm. 15(2):165-185 (1989).
Goto et al., J. Microencapsulation 5(4):343-360 (1988).

ART-UNIT: 152

PRIMARY-EXAMINER: Page; Thurman K.

ASSISTANT-EXAMINER: Harrison; Robert H.

ATTY-AGENT-FIRM: Sterne, Kessler, Goldstein & Fox

ABSTRACT:

The invention relates to a liquid methacrylic acid copolymer composi that contains a release adjusting agent and a pharmacological agent. composition forms a solid film upon drying, and is capable of accomplishing the sustained release of the pharmacological agent suc to permit its use in the treatment or prevention of dental or dermatological conditions.

18 Claims, 33 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 30

BRIEF SUMMARY:

FIELD OF THE INVENTION

The invention is directed to a liquid polymer composition which may used in the treatment or prevention of dental or dermatological cond such as fungal, bacterial, or viral infection, tooth hypersensitivit The composition provides a sustained release of an active agent whic be an antiseptic, an antibiotic, a viricidal agent, or any other pharmacological agent.

BACKGROUND OF THE INVENTION

I. Dental Conditions

A. Prevention of Plaque Formation, Caries, and Periodontal Disease

The relationship between bacterial plaque and the development of periodontal disease and caries has been thoroughly established (Axel P., et al., J.Clin. Perio. 5:133-151 (1978)). Periodontal disease is major problem in humans, especially in adults 40 years of age or old the mentally retarded, and in the handicapped. For the latter two gr in particular this is due to an inability to properly care for the t Periodontal disease is also widespread among animals, especially housepets. It has also been clearly shown that the bacterial flora o gingival crevice is important in the etiology of periodontal disease (Slots, J., J. Clin. Perio. 6:351-382 (1979)). Therefore, treatment periodontal and caries diseases is directed to controlling this flor

The most widely used approach to data has been mechanical cleaning m such as tooth brushing. Although this method has proved to be fairly successful in treating individuals, there is still a high recurrence There is also the problem of motivating people to good oral hygiene

that they will maintain throughout their lives.

Although systemic administration of antibiotics has been shown to be useful method of controlling the subgingival flora, discontinuation therapy will result in the return of the potential pathogens to the pockets (Genco, R.J., J. Perio. 52:545-558 (1981)). Long-term antibi therapy has been used, but the potential dangers associated with thi of treatment, which include the development of resistant strains and superimposed infections, do not warrant its serious consideration.

Antibacterial agents such as chlorhexidine and quaternary ammonium s in the form of mouth rinses, dentifrices, solutions and gels have no proven to be successful in preventing periodontal disease (see, for example, Ciancio, S.G., et al., Pharm. Therap. Dent. 3:1-6 (1978)), these agents are unable to affect the subgingival flora when adminis in these forms (Goodson, J.M., et al., J. Clin. Perio. 6:83-92 (1979 addition, reported side effects of chlorhexidine, including staining altered taste sensation, have resulted in limited usage. Attempts to reduce the staining and bitter taste by using dilute solutions and flavoring agents, respectively, have been only partially successful.

Sustained release has been reported to be achieved by embedding chlorhexidine in an ethyl cellulose polymer to form a film (Friedman et al., J. Perio. Res. 17:323-328 (1982); Friedman, M., et al., IADR and Abstr. 59:No. 905 (1980)). This dosage form was used in the loca treatment of periodontal disease (Soskolne, W.A., et al., J. Perio. 18:330-336 (1983)) and in the treatment of plaque prevention in pati wearing orthodontic appliances (Friedman, M., et al., J. Dent. Res. 64:1319-1321 (1985)). A drawback to this plaque preventative system that although plaque accumulation was decreased by the application o film composed of chlorhexidine embedded in an ethyl cellulose polyme effectiveness of the system in decreasing plaque accumulation was pr only for a period of four days subsequent to administration of the f Friedman, M., et al., (J. Dent. Res. 64:1319-1321 (1985)), concluded "clearly the conditions in the oral cavity and the formulation used not, at present, facilitate such prolonged prevention of plaque accumulation." These authors also suggested that by altering the fil components and method of preparation it might be possible in clinica to sustain the necessary level of antibacterial agent release for lo periods. No suggestion was made in this publication as to how this c be accomplished.

Other antibacterial preparations for plaque prevention have been disclosed. Gaffar (U.S. Pat. No. 4,339,430) discloses an antibacteri oral composition containing an agent such as bisbiguanidohexanes or quaternary ammonium salts, and an additive which reduces staining of dental surfaces such as copolymers of glutamic acid, tyrosine, and alanine. This preparation was reported to be applied as a mouthwash a toothpaste.

Wahmi (U.S. Pat. No. 4,374,824) disclosed dentifrices for cleaning a preserving teeth. Disclosed were compositions comprising ginger, mag silicate, sodium chloride, catechu, alum, seed and shell of sweet al pyrethrum, gum mastic, and tobacco. It was reported that gum mastic added to the composition to assist in the prevention of tooth decay. disclosed compositions were intended to be in the form of toothpaste tooth powders. This patent does not disclose the possible long-term

anti-plaque effect of the compositions; further, application of the disclosed compositions two to three times per day is required for anti-plaque activity.

Mastic has been used previously for other dental purposes. U.S. Pat. 4,668,188 (Wolfenson, G.B.) discloses the use of a curable mastic in production of an oral impression tray for making impressions of teet jaw structures. Mastics have been used in the production of dental m (U.S. Pat. No. 4,500,288, Von Weissenfluh, H.) and as an adhesive to secure dental articulators (U.S. Pat. Nos. 4,548,581 and 4,382,787, Hoffman, R.E.). U.S. Pat. Nos. 4,532,126 and 4,428,927 (Ebert, W.R., al.) disclose chewable, filled, one-piece soft elastic gelatin capsu made chewable by a masticatory substance, such as a synthetic mastic

U.S. Pat. No. 4,459,277 (Kosti, C.M.) relates to novel anti-plaque compositions for use in evaluating oral hygiene practices. In brief, patent discloses a water-insoluble, water-immiscible dye emulsified fine droplets or rupturable capsules. The patent discloses the use o mastic resin as well as alginates, and other gums as an insoluble me for dye dispersion. In particular, sodium carboxymethylcellulose is disclosed. Also disclosed is the possibility of incorporating antibacterial agents such as stannous fluoride into the compositions Significantly, the Kosti patent is concerned with diagnostic rather therapeutic applications. The patent fails to suggest compositions exhibiting long-term plaque preventive activity.

U.S. Pat. No. 3,956,480 (Dichter et al.) discloses the use of an ani polymer to sorb a cationic germicidal polymer to a tooth surface.

A topical, sustained-release form of an antibacterial agent could he prevent the above-discussed side effects. Such a dosage form would b to release the drug at a lower therapeutic level over a long period time and thus might prevent the bitter taste and tooth staining.

B. Treatment of Tooth Hypersensitivity

Dental hypersensitivity, especially that arising from dentin and cem hypersensitivity, is a frequently encountered problem in dentistry a very troublesome clinical complaint. Hypersensitivity may occur wher the dentin or cementum of a tooth is exposed by attrition or abrasio when the tooth's fine root surface is exposed by periodontal disease about 12% of erupted teeth, there is a developmental lack of protect covering of cementum at the cementoenamel junction. As a result, whe exposed dentin is subjected to mechanical, thermal, chemical or osmo stimuli, the sensory nerves of the teeth become excited and a very p response results. For example, people with hypersensitive teeth find very painful to orally ingest certain forms of nourishment, such as liquids or foods that are hot or cold, sweet, hypertonic or contain acid. Everyday stimuli such as brushing the teeth may also be painfu

Many attempts have been made to control hypersensitivity of the teet example, U.S. Pat. No. 3,863,006 (Hodosh, M.) describes the use of potassium, lithium or sodium nitrate; U.S. Pat. No. 4,751,072 and U. Pat. No. 4,631,185 (both to Kim, S.) describe the use of potassium bicarbonate and potassium chloride; U.S. Pat. No. 4,710,372 and U.S. No. 4,634,589 (both to Scheller, H.U.) describe the use of hydroxyap or fluorapatite; U.S. Pat. No. 4,057,621 Pashley, D.H., et al.) desc

the use of an alkali metal or ammonium oxalate; U.S. Pat. No. 4,415, (Shah, N.B.) describes the use of strontium EDTA, fluoride and ammon glycyrrhizzinate; and, GB patent No. 990957 (Rosenthal, M.W.) descri the use of strontium for the control of hypersensitivity. The use of strontium ions to treat hypersensitivity was also disclosed in U.S. Nos. 3,122,483, 3,988,434 and 4,224,310.

However, although clinically the most effective for reducing tooth hypersensitivity, the use of strontium salts for the treatment of hypersensitivity is disliked by patients due to the tendency of stro salts to leave an unacceptably salty taste or metallic taste in the even when used in a toothpaste form. Another major disadvantage of strontium dentifrice is the long period of time of application which required to achieve the clinical effect.

A topical, sustained-release form of an agent capable of controlling dental hypersensitivity could help prevent undesirable taste side ef and still treat the hypersensitive condition. Such a dosage form wou able to release the agent controlling the hypersensitivity at a lowe therapeutic level over a long period of time, for example, for weeks Sustained localized release of the hypersensitivity agent, targeted directly to the hypersensitive site, would also solve the problem of prolonged time and application currently required to obtain clinical effectiveness with strontium.

C. Root Canal Sterilization

A major concern in root canal dental procedures is the possibility. o infection due to the introduction or cross-infection of bacteria, et into the affected region. Various surgical and endodontic methods ha been developed in order to minimize the risk of infection (Miserendi L.J., Oral Surg. Oral Med. Oral Pathol. 66:615-619 (1988); Mondragon E.J., Pract. Odontol. 8:16-22 (1987); Hermsen, K.P. et al., Gen. Den 35:355-356 (1987); Levy, G. et al., Zahnarzt 30:441-442, 447-450 (19 Chivian, N., Dent. Clin. North Amer. 28:637-649 (1984); Linke, H.A. al., Oral Surg. Oral Med. Oral Pathol. 55:73-77 (1983); Agarwal, S.K al., J. Indian Dent. Assoc. 54:323-326 (1982), which references are incorporated herein by reference). Camphorated parachlorophenol (CPK an antibacterial agent used to treat bacterial contamination in the canal. The usual treatment involves dipping an absorbent point or ga into a CPK solution and placing it in the root canal. The absorbent remains in the root canal until the next visit to the dentist. The p disadvantage of the current treatment is the limited exposure time o active material which may lead to re-infection of the root canal.

II. Fungal Infections

Microfungi can be classified as yeasts and filamentous fungi. Microf are capable of causing a variety of diseases in the oral cavity and surrounding area. Mycotic diseases may arise as part of a systemic microfungal infection or may be derived from an independent infectio which establishes in the oral cavity. Oral mycoses and their treatme an important problem in oral medicine and have been reviewed in Kost I. et al., Acta Odontol. Scand. 37:87-101 (1987), incorporated herei reference.

Many factors can predispose a patient to an opportunistic microfunga

infection in the oral cavity. For example, general debilitation or p oral hygiene are predisposing factors. Patients who are being treate antibiotics, steroids, or cytostatic therapy, patients with AIDS, di mellitus or other immunodeficiency or hormonal diseases, patients wi malignant tumors or a hematogenous disorder are a high risk for opportunistic fungal infections. In addition, certain age groups suc infants, the elderly, and pregnant women are at a higher risk of ora fungal infections.

Mechanical trauma from an ill-fitted prosthesis is also a major caus oral microfungal infections. One report estimated that Candida was involved in 60% of the cases of "denture sore mouth" (denture stomat in the elderly (Budtz-Jorgensen, E. et al., Community Dent. Oral Epidemiol. 3:115 (1975)). Denture stomatitis appears to be a manifes of a cell-mediated hypersensitivity reaction to the microfungal infe

It is important to treat oral mycotic infections as soon as possible Untreated infections may become the foci for systemic dissemination yeast or fungus, with potentially fatal result in severely compromis patients. For example, disseminated candidiasis is the second most c opportunistic infection in patients with AIDS (Odds, F.C., CRC Crit. Microbiol. 15:1-5 (1987)).

The most important species of microfungi which have been implicated being involved in superficial or deep mycotic infections in the oral cavity include Candida albicans, C. tropicalis, C. stellatoidea, C. pseudotropicalis, C. parapsilosis, C. guilliermondii, C. krusei, and vixwanathii, all of which have been implicated in candidiasis; Torul glabrata which is the cause of torulpsidosis; Geotrichum candidum, w is the cause of geotrichosis; Rhizopus, Mucor, Absidia, and Basidiob which are the cause of aspergillosis, Cryptococcus neoformans, the c of cryptococcosis; Blastomyces dermatitidis, the cause of blastomyco Paracoccidioides brasiliensis, the cause of paracoccidioidoymcosis; Sporothrix schenkii, the cause of sporotrichosis; Rhinosporidium see the cause of rhinosporidoisis; Histoplasma capsulatum, the cause of histoplasmosis; Histoplasma duboisii, the cause of African histoplas Coccidiodes immities, the cause of coccidioidoymcosis, Trichophyton mentagrophytes, T. rubrum, T. tonsurans, and T. violaceum, the cause dermatophytosis; and, Rhinocladiella or Phialophora, and Cladosporiu causes of chromomycosis.

The Candida species is the most virulent of the fungi which infect t oral mucosa. Pathogenic Candida species are aerobic yeasts that can grow anaerobically. C. albicans, the Candida species most often responsible for infections of the oral cavity, grows in two morpholo forms: either as a budding yeast, or as a continuously extending hyp which extends into tissue. In the oral cavity, Candida may cause a v of disorders based on localization of the infection such as pulpitis gingivitis, tonsillitis, cheilitis, glossitis, stommatitis, pharyngi laryngitis and sinusitis.

Oral candidiasis has been classified into different categories based the clinical and histopathological manifestations of the infection (Lehner, T., in Clinical Aspects of immunology, P.G.H. Gell, et al., 3rd edition, Blackwell Scientific Publications, Oxford, 1975, pp. 1387-1427).

Acute pseudomembranous candidiasis, or thrush, primarily affects chi or patients with debilitating diseases (Crawson, R.A., Dent. Res. 15:361-364 (1965). C. albicans is a major causative agent of thrush newborn.

The clinical signs which usually appear first are creamy-white, soft nonkeratotic plaques which appear on the mucosa of the tongue, cheek and pharynx. The plaque is easily rubbed off, leaving an inflamed mu underneath. There may be no subjective symptoms until the plaque spr to the pharynx, larynx or esophagus, where it may cause dysphaghia, soreness and dryness of the tongue, a sore throat or symptoms of cheilitis.

Acute atrophic candidiasis is a form of thrush which is consistently painful, and which is through to arise as a consequence of the shedd the fungal plaque from its site of attachment to the tissue. It can found on the dorsum linguae, or associated with angular cheilitis an inflammation of cheeks and lips.

Chronic atrophic candidiasis, or denture stomatitis is the term give Candida-based infections of the denture-bearing tissues. Torulopsis glabrata is also associated with some forms of denture stomatitis.

Chronic mucocutaneous candidiasis refers to four different types of candidiasis which are resistant to treatment and which are associate patients with a herterogeneous pattern of immunodeficiencies. These of candidiasis include chronic oral hyperplastic candidiasis, which predominately affects adult males between the ages of 30 and 70; chr localized mucocutaneous candidiasis, which starts in childhood as an intractable oral Candida infection and later manifests itself as les in the nails, and skin of the fingers and toes; chronic localized mucocutaneous candidiasis with granuloma which primarily affects you girls, starting in the mouth but later manifesting itself as horny m of the face, scalp and upper respiratory tract; and, chronic localiz mucocutaneous chadidosis with endocrine disorder, also found most frequently in young girls, and associated with lesions of the tongue cheek, oral commissures and nails.

The establishment of a mycotic infection in the oral cavity presents serious health problem to the host which must be treated and contain Treatment of mycotic diseases is directed to controlling this flora.

The most widely used approach to data to control microfungi in the o cavity has been mechanical cleaning methods such as brushing the tee Although this method has proved to be fairly successful in treating individuals, there is still a high recurrence rate. There is also th problem of motivating people to good oral hygiene habits that they w maintain throughout their lives.

Systemic administration of antimycotics per os or intravenously has used to control mycotic infections, however, discontinuation of ther often results in the return of the pathogens to the oral cavity. Lon systemic antimycotic therapy in doses high enough to control oral infections are undesirable for treatment of oral infections because potential dangers and side-effects associated with this form of trea include the development of resistant strains and superimposed infect

gastrointestinal irritation, liver damage and neurological symptoms, others.

Ridgway, F. et al., U.S. Pat. No. 4,725,440, describes a soft, anti-drug-containing pastille or troche which is free of rough edges and not adhere to oral mucosa, but which only releases anti-fungal medic within the 15-90 minutes while it dissolves in the mouth.

Cyr et al., U.S. Pat. No. 3,312,594 describes long lasting troches o pastilles for the treatment of oral lesions which include an anhydro adhesive based on pectin, gelatin and carboxymethylcellulose and whi when wetted, adhere to the oral mucous membranes. However, the Cyr formulation was not well-tolerated by patients (Ridgway, F. et al., Pat. No. 4,725,440).

Antifungal agents have also been used in the form of mouth rinses, dentifrices, solutions and gels but have not proven to be completely successful in preventing fungal infections. A main problem with thes techniques is that the antifungal drug does not remain in the oral c long enough at efficacious levels.

Another serious problem with antifungal drugs is that they are by necessity directed towards controlling an infection by a eukaryotic cell in a eukaryotic host. As a result, drugs effective against the also tend to be toxic to the host. Thus is it important to develop m which permit the localized, sustained application of the toxic drug manner and dosage which is efficacious but which minimizes toxicity host. Especially, it is important to develop methods which use low d of the drug.

III. Dermatological Conditions

A dermatological disease or condition is one which affects the skin. conditions may reflect either the reaction of the immune system to a particular antigen or allergen, as is the case in rashes associated allergic contact dermatitis (such as a reaction to poison ivy, poiso bee venom, etc.). Other dermatological conditions are caused by a va of inflammatory causes (such as exfoliative dermatitis, eczematous dermatitis, pustules, psoriasis, urticaria, erythema multiforme synd purpura, etc.). Yet other dermatological conditions may reflect bact infection (such as insect bites, impetigo, acne vulgaris, Lyme disea lesions, etc), fungal infection (such as ringworm, tinea versicolor, cutaneous candidiasis, molluscum contagiosum, etc.) or viral infecti (such as warts, herpes simplex or zoster lesions, chicken pox lesion rubella macules or papules, etc.).

Yet another type of dermatological condition of concern to the prese invention are burns, and especially sunburn.

IV. Summary

The background art thus fails to identify any compositions of matter comprising a sustained-release carrier which can be used in conjunct with a bacteriocidal agent, for use as a sustained plaque preventati humans and other animals, under conditions in which the agents have deleterious medical side effects, and do not cause staining of the t

The background art also fails to identify any compositions of matter comprising an effective anti-hypersensitivity agent together with a term sustained release carrier capable of providing efficacious leve the anti-hypersensitivity agent, for use as a hypersensitivity preventative by humans and other animals, under conditions in which anti-hypersensitivity agents have no undesirable side effects such a changes in taste sensations.

A topical, sustained-release form of an antifungal agent, could help maintain a locally efficacious level of the antifungal drug in the o cavity and prevent these side effects. Such a dosage form might also prevent undesirable systemic side effects by releasing the drug at a therapeutic level over a long period of time in a localized manner.

A need therefore exists for a composition comprising a sustained rel carrier which could be used in conjunction with an antifungal, antib antiseptic, antiviral or other pharmacological agent, for use in the sustained release of such agent(s) in the prevention or therapy of d dermatological (and other) conditions of humans and other animals. I particularly desirable that the antibacterial agent should be releas from the composition, not only in a sustained fashion, but over a sufficiently long period of time so as not to require excessive application of the composition.

SUMMARY OF THE INVENTION

With the above-described needs in mind, the present inventors set ou find a composition which could be adapted to accomplish the sustaine release of a pharmacological agent such as to permit its use in the treatment or prevention of dental or dermatological conditions.

When attempting to use dental or dermatological agents in a liquid p composition consisting of methacrylic acid copolymer, two principal problems are encountered: (1) the hydrophilic nature of the copolyme causes rapid disintegration of the film, and in parallel, causes rap release of the active agent; and (2) some agents may interact with t copolymer making it hydrophobic in nature, thus almost totally preve release of the active agent from the film and slowing the disintegra process (i.e., nondegradable film).

These problems have prevented the use of such a polymer as a matrix the controlled release of drugs to treat dental or dermatological conditions.

The invention has, for the first time, solved these problems and, fo first time, allowed dental and dermatological agents to be provided subject in a controlled or sustained release manner in conjunction w acrylic polymers.

Of particular concern to the present invention are oral conditions, including both conditions that are directly related to dental and periodontal disease (such as plaque, dental caries, periodontal dise root canal infections, tooth extractions, tooth hypersensitivity, et and conditions that are not directly related to dental and periodont disease (such as oral candidiosis, pizza burns, tumors, aphthous ulc abscesses, denture stomatitis, halitosis, etc.), and including denta esthetics (tooth whitening, etc).

The dermatological conditions of concern to the present invention in fungal infections, bacterial infections, viral infections, burns, in bites, impetigo, tumors, etc.

Of additional concern in the present invention is a composition and of controlling the delivery of bone growth factors or alternatively providing an occlusive membrane over a damage bone and/or tissue, th enhancing the regenerative process.

In detail, the invention provides a sustained-release liquid polymer composition which comprises:

(a) a sustained release acrylic polymer;

(b) a release adjusting agent (herein termed a "RAA"); and

(c) a pharmacological agent;

in a pharmaceutically acceptable vehicle, wherein the sustained rele acrylic polymer is selected from the group consisting of EUDRAGIT L, EUDRAGIT S, EUDRAGIT RL, and EUDRAGIT RS.

The invention further concerns the embodiment of the above-described composition wherein the pharmacological agent is selected from the g consisting of: an antibiotic, an antiseptic, an anti-fungal agent, a anti-viral agent, a bone and/or tissue growth factor, an anti-tumor an anti-inflammatory agent and a hypersensitivity agent.

The invention also concerns the embodiment of the above-described composition wherein the pharmacological agent is a bacteriocidal quaternary ammonium salt such as cetylpyridinium chloride or benzalk chloride or other bacteriocidal agent such as camphorated p-Chloroph (CPK).

The invention also concerns the embodiment of the above-described composition wherein the pharmacological agent is a hypersensitivity (for example, a strontium salt such as strontium chloride or stronti citrate), a potassium salt (such as potassium chloride, potassium hy tartrate, or potassium nitrate), a fluoride (such as stannous fluori or oxylates (such as potassium hydrogen oxylates).

The invention also concerns the embodiment of the above-described composition wherein the pharmaceutically acceptable vehicle comprise agent selected from the group consisting of water; ethyl alcohol; an ethyl alcohol and water.

The invention also concerns the embodiment of the above-described composition which additionally contains a plasticizer, or polyethyle glycol or dibutyl phthalate.

The invention also concerns the embodiment of the above-described composition where the release adjusting agent is selected from the g consisting of: a cross-linking agent, a polysaccharide, a lipid, a polyhydroxy compound, a protein such as Byco E or Byco C and an amin (for example, arginine or lysine), or a combination of the above rel adjusting agents.

The invention also provides a method of oral plaque prevention compr topical application of the aforementioned liquid polymer composition the teeth or gingival tissues of an animal or human.

The invention also provides a method of treating oral infection comp topical application of the aforementioned liquid polymer composition the oral cavity of an animal or human.

The invention also provides a method of treating tooth hypersensitiv comprising topical application of the aforementioned liquid polymer composition to the teeth or gingival tissues of an animal or human.

The invention also provides a method of achieving root canal sterili comprising topical application of the aforementioned liquid polymer composition to the teeth or gingival tissues of an animal or human.

The invention also provides a method of treating a dermatological di or condition comprising topical application of the aforementioned li polymer composition to the skin of an animal or human.

The invention also provides a method of treating a dermatological di or condition comprising topical application of the aforementioned li polymer composition to a mucosal tissue of an animal or human.

The invention also provides an absorbent point, gauze, or film in combination with a controlled-release composition containing a liqui polymer and an active agent, especially CPK.

DRAWING DESCRIPTION:

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the cumulative release percentage of cetylpyridinium ch (CPC) from the films produced by the drying of 5 liquid polymer compositions.

FIG. 2 shows the cumulative release percentage of CPC from the films produced by the drying of 4 liquid polymer compositions.

FIG. 3 shows the cumulative release percentage of CPC from the films produced by the drying of 7 liquid polymer compositions.

FIG. 4 shows the cumulative release percentage of CPC from the films produced by the drying of 5 liquid polymer compositions.

FIG. 5 shows the cumulative release percentage of CPC from the films produced by the drying of 4 liquid polymer compositions.

FIG. 6 shows the cumulative release percentage of CPC from the films produced by the drying of 4 liquid polymer compositions.

FIG. 7 shows the cumulative release percentage of CPC from the films produced by the drying of 4 liquid polymer compositions.

FIG. 8 shows the cumulative release percentage of CPC from the films

produced by the drying of 5 liquid polymer compositions.

FIG. 9 shows the cumulative release percentage of CPC from the films produced by the drying of 6 liquid polymer compositions.

FIG. 10 shows the cumulative release percentage of CPC from the film produced by the drying of 4 liquid polymer compositions.

FIG. 11 shows the cumulative release percentage of CPC from the film produced by the drying of 3 liquid polymer compositions.

FIG. 12 shows the effect of polyethylene glycol ("PEG") on the relea strontium chloride from a film produced by the drying of a liquid po composition.

FIG. 13 shows the effect of polyethylene glycol ("PEG") on the degra of 4 films produced by the drying of a liquid polymer composition.

FIG. 14 shows the effect of trisodium citrate on the ability of a fi release strontium.

FIG. 15 highlights the effect of the addition of trisodium citrate a also shows that the inclusion of PEG increased the rate of strontium release from citrate-containing films as it did for films without ci

FIG. 16 shows that the degradation rate of a film was increased by P but appeared to be unaffected by trisodium citrate.

FIG. 17 shows the effect of the concentration of trisodium citrate i film on the strontium release profile.

FIG. 18 shows the effect of the concentration of trisodium citrate i film which additionally contains calcium chloride on the strontium r profile.

FIG. 19 shows the in vitro release of p-chlorophenol from film cast formulations RK25.2-4.

FIG. 20 shows the in vitro release of p-chlorophenol from formulatio RK25.1-4 from coated absorbent points.

FIG. 21 shows the in vitro release of p-chlorophenol from absorbent points-polymer systems RK25.3 and RK25.5.

FIG. 22 shows the in vitro release of p-chlorophenol from polymer ma systems.

FIG. 23 shows the in vitro release of p-chlorophenol from metacrylic copolymer matrix systems.

FIG. 24a shows the effect of CaCl.sub.2 on the in vitro release of chlorophenol from polymer film.

FIG. 24b shows the effect of CaCl.sub.2 on the in vitro release of chlorophenol from polymer film.

FIG. 25 shows the effect of CaCl.sub.2 on the in vitro release of chlorophenol from polymer-coated paper tissues.

FIG. 26a shows the in vitro release of p-chlorophenol from polymer-c paper tissues.

FIG. 26b shows the in vitro release of p-chlorophenol from polymer-c paper tissues.

FIG. 27 shows the in vitro release of p-chlorophenol from polymer-absorbent point (AP) systems.

FIG. 28a shows the in vitro release of p-chlorophenol from CM-103.

FIG. 28b shows the in vitro release of p-chlorophenol from CM-103.

FIG. 29 shows the bacterial growth inhibition of CPK-AP (labeled as CCP-AP) systems.

FIG. 30 shows the cumulative release of cetyl-pyridinium chloride (C from liquid polymer films as a function of the presence of arginine.

DETAILED DESCRIPTION:

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following names are used in this application and are trademarks: EUDRAGIT.TM., Byco.TM., Teflon.TM., UVIKON.TM., Kimwipes.TM., Teflon Tween 80.TM., and Dentsply.TM..

I. The General Nature of the Liquid Polymer Composition

The present invention concerns a composition comprising a non-biodegradable, liquid polymer (referred to as a "varnish" in U.S patent application Ser. No. 07/369,223). The composition may be desi to be degradable or non-degradable. By a composition which is degrad but non-biodegradable is meant a composition which is slowly solubli but which is resistant to enzymatic degradation in vivo. By a compos which is non-degradable is meant a composition which is neither solu nor biodegradable.

The invention is derived, in part, from the inventors' discovery tha properties of liquid polymethacrylate polymers, and especially of EUDRAGIT, can be altered to allow for their use as in oral and denta compositions. Specifically, the invention is derived, in part, from inventors' discovery that such polymers can be altered to be less hydrophilic and more hydrophobic. Further, the invention is derived, part, from the inventors' discovery that such polymers may be altere provide a controlled, sustained-release of an active agent by the inclusion of a release adjusting agent. As a result of these alterat the rate of release of active agents is controlled in a manner desir for oral and dental use. Compositions containing such polymers may therefore be used to provide efficacious levels of a dental or dermatological agent to a subject in need of such treatment.

In a preferred embodiment, the liquid polymer composition of the inv

further contains one or more desired "pharmacological agents" whose sustained release is desired. Such agents may include an anti-fungal antibiotic, antiseptic, antiviral, anti-inflammatory, anti-tumor, or pharmacological agent, bone growth factors, tissue growth factors, a salt or other agent to treat tooth hypersensitivity, or, in general, agent suitable for treating a dental and/or dermatological condition

In a preferred embodiment, the release adjusting agent is selected f (1) a cross-linking agent, (2) a polysaccharide, (3) a lipid, (4) a polyhydroxy compound, (5) a protein such as Byco E or Byco C, (6) an acid, or (7) a combination of the above release adjusting agents.

The agent(s) is embedded in a sustained release carrier composed of polymer. Suitable polymers include an acrylic polymer, a hydrophilic acrylic polymer, a hydrophobic acrylic polymer, or a combination of acrylic polymers, in a pharmaceutically acceptable vehicle.

The carrier may optionally, and preferably, contain one or more agen such as a plasticizer (such as polyethylene glycol, dibutyl phthalat etc.).

In additional, the composition may contain an adhesive polymer (such gum mastic, etc.), or a flavorant, and/or a coloring agent. It is additionally possible to include anti-inflammatory agents, analgesic anesthetics into the composition so as to relieve or prevent inflamm lessen pain, etc.

The compositions of concern to the present invention are termed "liq polymer" compositions. Such compositions are liquids which (by polymerization, evaporation, etc.) become solidified to produce a fi accordance with the present invention, such films have the capacity release a desired pharmacological agent, and thereby provide treatme for, or prevent, a particular disease or condition. The solidified f are capable of releasing the pharmacological agent over a substantia period of time (i.e., hours or months, depending upon the compositio Thus, such films are sustained release devices.

The "liquid polymer" composition of the present invention is a compo which is preferably topically applied to a surface such as a tooth, skin, to a mucous membrane (oral, vaginal, rectal, etc.), and the li by brush, spray, etc., and which dries as a film adhering to that su in a manner which resists removal under normal conditions, such as e or brushing, for applications to the teeth and oral mucosa, or norma washing and abrasion, when applied to skin. Alternatively, the compo may be applied to bandages, dressings, gauze, brushes, implants, etc permitted to dry into a film in advance of its administration to a patient. Although the solidified liquid polymer composition is refer as a "film," it is to be understood that the thickness of the film m varied or increased by multiple applications of the liquid polymer. for example, it is possible to produce a "film" which can fill wound cuts, abscesses, tooth sockets, etc.

The release adjusting agent ("RAA") is an agent whose presence in th liquid polymer composition serves to adjust the release rate of the pharmacological agent. As indicated above, it may be a cross-linking (such as glutaraldehyde, citric acid, lysine, aspartic acid, glutari acid, etc.), or a polysaccharide (such as dextran, etc.), or a lipid

as sodium docusate, etc.), or a polyhydroxy compound (such as polyet glycol, glycerol, propylene glycol), or a protein such as Byco E or C.

For use in the treatment of tooth hypersensitivity, a preferred RAA sodium citrate which is used to control the release of strontium fro dried film; the concentration of sodium citrate in the film controls release rate of the strontium. Sodium docusate is an alternative RAA tooth hypersensitivity uses of the liquid polymer composition of the present invention. RAA are preferably provided to those liquid polym compositions which are to be used for dermatological uses as a means compensating for the lack of humidity in the skin.

By "oral cavity" is meant the mouth and the surrounding esophageal a Therefore, for example, the oral cavity includes the tongue, gums, p throat teeth, tonsils and periodontal tissue.

By "sustained-release" is meant the continuous release of an active substance at efficacious levels for a prolonged period of time, such for one hour or longer for the case of plaque prevention, or as much 2-4 weeks or longer for other purposes. The release of the active substance may be constant or pulsed, as long as efficacious levels o active substance are provided to the surrounding milieu for the desi period of time.

The pharmacological agents of the liquid polymer compositions of the present invention include any of a wide variety of antibacterial age antifungal agents, and antiviral agents, as well as agents for root sterilization, antisepsis, or for the treatment of tooth hypersensit As used herein, the term "antibacterial agent" includes both bacteri and bacteriostatic agents. Such agents are, as indicated above, effe in the treatment or prevention of oral or dermatological diseases an conditions. An agent is said to be effective in the treatment of a d or condition, if its administration to a patient exhibiting the dise condition results in a decrease in the severity or duration of the d or condition. Likewise, an agent is said to be effective in the prev of a disease or condition, if its administration to a patient at ris the disease or condition results in a decrease in such risk.

By an "effective" or "efficacious" level is meant a level or concent of a drug or other active agent which is high enough to be effective treating the condition the drug was designed to treat. The particula formulation of the liquid polymer composition will, thus, determine particular use for which it is suitable.

Of particular interest to the present invention are liquid polymer compositions containing anti-fungal, antibacterial, or anti-viral ag or growth promoting agents for bone and/or tissue. When used for ora dermatological purposes, any topically applicable or systemically tolerated antiseptic or antibiotic may be empolyed. Suitable agents described in Goodman and Gilman's The Pharmacological Basis of Therapeutics, A.G. Gilman et al. (eds.), Macmillan Publ. Co., N.Y. (which reference is incorporated herein by reference).

A variety of antifungal agents are suitable for the present inventio Preferred are the polyene antifungals, especially nystatin and amphotericin B. Examples of other antifungal agents applicable to th

methods of the invention include 5-fluorocytosine and imidazole- and triazole-derivative antifungal agents, especially naftifine, terbina tolnaftate, tolciclate, isoconazole, sulconazole, miconazole, clotrimazole, econazole, bifonazole, oxiconazole, tioconazole, ketoconazole, miconazole nitrate, itraconazole, fluconazole, and terconazole, all known to the art. See, for example, Kostiala, I. et Acta Odontol. Scand. 37;87-101 (1979). Additional anti-fungal agents may be employed include amphotericin B, nystatin, flucytosine, griseofulvin, hydroxystilbamine isethionate, derivatives of undecyle benzoic, propionic, caprylic or salicylic acid, ciclopirox olamine, haloprogin, hexylresourcinol and its derivatives (such as acrisorcin etc.), natamycin, carbol-fushin, resorcinol, sulfur, aminacrine hydrochloride, gentian violet, iodine, iodoquinol and clioquinol, et

In another embodiment, combinations of more than one antifungal agen used in the composition of the invention. Combinations of antifungal agents can for the purpose of providing treatment or protection agai broad spectrum of microfungal species, or for the purpose of attacki specific microfungal species with drugs acting through different mod action. Combination of antifungal agents may also allow a lower dose given antifungal agent to synergistically act with a lower dose of a antifungal agent in a manner which is efficacious in combination but separately.

Examples of suitable antibacterial agents which may be employed in accordance with the present invention include the pencillins and ampicillins, clindamycin, erythromycin, tetracycline, vancomycin, chloramphenicol, trimethoprim, aminoglycosides (such as gentamycin, streptomycin, neomycin, kanamycin, etc.), polymyxin B, etc.

Examples of suitable antiviral agents which may be employed in accor with the present invention include acyclovir, idoxuridine, salicylic and its derivatives, amantadine, ribavirin, interferons, etc.

In addition to the above-described agents, non-specific disinfectant antiseptics may be employed in the liquid polymer compositions of th invention. Such agents may be used for the treatment of oral or dermatological diseases and conditions if their administration can b tolerated by the patient without unacceptable side effects. Examples suitable disinfectants include chlorhexidine (and especially chlorhhexidine digluconate), chlorine and chlorofors, iodine and iodophors, silver compounds (such as silver nitrate, silver sulfadia etc.) mercury compounds (such as merbromin, thimerosol, mercuric chl ammoniated mercury, etc.), zinc compounds (especially zinc oxide), nitrofurazone, phenols, anthralin, benzoyl peroxide, hydrogen peroxi quaternary ammonium compounds, etc. Cetylpyridinium chloride and benzalkonium chloride are preferred agents.

The liquid polymer compositions of the present invention may alterna contain photo-absorbing agents (such as para-aminobenzoic acid and t like) such that they may be used in the prevention of sunburn. Likew they may contain cosmetic agents (such as anti-wrinkle agents, moisturizing agents, etc), such that they may be used as cosmetics.

A "hypersensitivity agent" is an agent which is capable of treating hypersensitivity when provided in an effective amount to a recipient need of such treatment. Any of a variety of anti-hypersensitivity ag

are suitable for the present invention.

The liquid polymer compositions of the present invention may contain a single pharmacological agent, or they may have any number of agent such multiple agents may be of the same type (for example, all being anti-fungal agents), or they may be of different types (for example, antibacterial agent and an anti-fungal agent). Any combination of ag may be employed.

II. The Polymer of the Liquid Polymer Compositions

The sustained release of the above-described agents is, in accordanc the present invention, preferably accomplished by embedding the agen an acrylic polymer, or a hydrophilic acrylic polymer, or a hydrophob acrylic polymer or a combination of such acrylic polymers, in the pr of a release adjusting agent, to form a liquid polymer composition w is compatible with tissues in the oral cavity and with dermatologica

Polymers of special interest to the present invention include hydrop polymers such as polymethacrylates containing more than 50% methacry acid monomers, relatively hydrophilic polymers such as polymethacryl containing quaternary amine groups, and combinations of such hydroph and hydrophobic polymers in various ratios.

EUDRAGIT is a non-biodegradable, polymethacrylate polymer (Roehm Pha GmbH, Darmstadt, Federal Republic of Germany) which may be formulate disintegrate or dissolve in water, saliva, etc. EUDRAGIT exists in f forms: S, L, RS and RL (Drugs and the Pharmaceutical Sciences vol. 3 McGinity, J.W. (ed.), Marcel Dekker, Inc., N.Y. (1989); Chafi, N. et Drug Dev. Ind. Pharm. 15:629-648 (1989); Chang, R.K., et al., Drug. Ind. Pharm. 15:361-372 (1989); Thoennes, C.J. et al., Drug. Dev. Ind Pharm. 15:165-186 (1989); Silva, J.F.P.D. et al., Folha Med. 97:253- (1988); Larroche, C. et al., Enzyme Microb. Technol. 11:106-112 (198 Rachmilewitz, D. et al., Brit. Med. J. 298:82-86 (1989); Goto, S. et J. Microencapsul. 5:343:360 (1988); which references are incorporate herein by reference).

EUDRAGIT RL and RS are water insoluble copolymers synthesized from a and methacrylic acid esters with a low content of quaternary ammoniu groups. These polymers form non-degradable or non-disintegrating fil more hydrophilic polymer is added to the film, such as EUDISPERT.RTM (Dittgen, M. et al., Pharmazie 41:883-884 (1987); Kristl, J. et al., Pharm. Technol. 33:140-144 (1987), which references are incorporated herein by reference), EUDRAGIT S or EUDGRAGIT L, a different sort o can be formed which could disintegrate.

EUDRAGIT L (or S) and EUDISPERT are anionic co-polymers based on methacrylic acid and methyl methacrylate. EUDISPERT L is soluble in solutions above pH 6.0. Due to the fact that EUDISPERT is a polycarb acid salt which could react with cationic drugs, it is not preferabl prepare films from liquid polymers containing EUDISPERT polymer alon EUDISPERT was used successfully as an additive, however, for alterin release from films. EUDRAGIT L, in contrast, formed nice and homogen films which degraded in phosphate buffer pH 6.8.

EUDRAGIT L is a methacrylic acid type A copolymer, an anionic copoly

based on methacrylic acid and methylmethacrylate wherein the ratio o carboxyl groups to the ester groups is approximately 1:1. EUDRAGIT S methacrylic acid type B copolymer, an anionic copolymer based on methacrylic acid and methylmethacrylate wherein the ratio of free ca groups to the ester groups is approximately 1:2. EUDRAGIT RL is a dimethylaminoethylacrylate/ethylmethacrylate copolymer, a copolymer on acrylic and methacrylic acid esters with a low content of quatern ammonium groups wherein the molar ratio of the ammonium groups to th remaining neutral (meth)acrylic acid esters is 1:20. EUDRAGIT RS is ethyl methacrylate/chlorotrimethylammoniumethyl methacrylate copolym copolymer based on acrylic and methacrylic acid esters with a low co of quaternary ammonium groups wherein the molar ratio of the ammoniu groups to the remaining neutral (meth)acrylic acid esters is 1:40.

Although all of the four forms of EUDRAGIT are hydrophilic, it is ha to dissolve the RL/RS forms, then the L/S forms, in saliva. Thus, fo and dental uses, it is therefore preferable to add a plasticizer (su for example, polyethylene glycol, dibutyl phthalate, etc.) to the RL form polymers in order to increase the rate of solubility of the R f in saliva.

In order to increase the rate of degradation, and to increase the re of drug, it is possible to add agents such as citric acid, lysine, aspartic acid, glutamic acid, glutaric acid, etc.

The EUDRAGIT S or EUDRAGIT L polymers are highly soluble in buffer solutions. Lysine, citric acid, and divalent cations of calcium, strontium, etc., are each capable of cross-linking EUDRAGIT S or EUD L polymers. Thus, such agents can be added to such polymers in order decrease the rate of dissolution of the polymer. For oral and dental purposes, the preferred polymers of the present invention are polymethacrylates such as EUDRAGIT.RTM. and EUDRAGIT(L). EUDRAGIT(R) the preferred polymer for dental and oral purposes. For dermatologic purposes, any of the four EUDRAGIT polymers may be employed (i.e. (S (L), (RL) and (RS)).

In another embodiment of the present invention, the compositions may contain additional desirable components. For example, if desired, th adhesiveness of the composition may be improved by the incorporation within said composition of gums such as gum mastic in a formulation providing from 1-20% by weight of the gum mastic. Other suitable mas are disclosed in U.S. Pat. No. 4,315,779 to Heyd, D., et al., and U. Pat. No. 4,374,844 to Wahmi, H.V.R., et al.

Likewise, the compositions may contain demulcents/humectants (i.e., plasticizers) such as polyethylene glycol 400-to-4000, glycerol, sor or mineral oil in concentrations of about 1% by weight. Other humect detergents, or surface-active agents will be known to those skilled formulation of oral compositions. Polyethylene glycols or dibutyl phthalate are the preferred optional plasticizers of the invention. agents play a role in enhancing the rate of degradation of the film improving its adherence.

For application to buccal or lingual surfaces of teeth, or to mucosa tissue, the liquid polymer (containing a suitable pharmaceutical age may be applied by spray, soft brush, etc. Solvent may be evaporated gentle stream of warm air, or by other means.

For application to orthodontic appliances, a total of about 70 mg of bacteriocidal agent, dissolved in polymer may be applied per applian with a soft brush or spray, and residual solvent removed with a gent stream of warm air.

Those skilled in the art will, without undue experimentation, be abl produce ranges of concentrations of appropriate agents and sustained release polymers.

III. Uses for the Liquid Polymer Compositions of the Invention

A. Oral and Dental Uses

The use of antibacterial and hypersensitivity agents, for dental pur in certain hydrophilic or acrylic polymer based sustained release compositions is disclosed in U.S. patent applications Ser. Nos. 07/189,918, and 07/304,091 which applications are herein incorporate reference.

The use of the above-described polymers of the present invention has advantage of minimizing side effects such as staining of teeth and dentures and unpleasant taste (see, for example, Friedman, M., et al Dent. Res. 64:1319-1321 (1985)). The liquid polymer compositions of present invention are intended for use in the treatment or preventio oral and/or dental diseases or conditions.

1. Plaque and Caries

Plaque and caries are among the dental diseases or conditions which treated or prevented through the use of the liquid polymer compositi the present invention. One preferred composition of the present inve for oral use contains an anti-plaque or anti-caries agent, and is de for oral use in the treatment of plaque or caries. An agent is an anti-plaque agent, or an anti-caries agent, if, when provided in an effective amount to a recipient, it is capable of preventing or attenuating the accumulation of plaque or caries. Preferred for such are the cationic nitrogen-containing antibacterial materials that ar known to the art. See, for example, the section on "Quaternary-Ammon and Related Compounds" in the article on "Antiseptics and Disinfecta in Kirk-Othermer Encyclopedia of Chemical Technology, 2nd ed. (Vol. 632-5), incorporated herein by reference. Such materials have been u oral compositions to counter plaque formation caused by bacteria in oral cavity. Among the most common and efficacious of these antibact anti-plaque quaternary ammonium compounds are cetylpyridinium chlori benzalkonium chloride. Other cationic ammonium antibacterial agents this type are mentioned, for instance, in U.S. Pat. Nos. 2,984,639, 3,325,402, 3,431,208, 3,703,583, and 4,339,430, British Patent No. 1,319,396, and German Patent No. 2,332,383. Most preferred is cetylpyridinium chloride, which is efficacious, compatible with the components of the oral composition, and inexpensive by virtue of bei non-prescription drug.

In yet another embodiment, the composition may contain an oxygenatin agent. Such as agent will be present in an amount capable an anti-ca anti-plaque or antiseptic-like effect. Examples of suitable oxygenat agents include urea peroxide, hydrogen peroxide (Cameron, J.A. et al

Austral. Dent. J. 29:80-85 (1984); Firestone, A.R. et al., Caries Re 16:112-117 (1982); Futaki, S. et al., Shikwa Gakuho 80:487-495 (1980 carbamide peroxide (Ullmann, E. et al., Somatol. DDR 33:334-341 (198 peroxyborate monohydrate (Addy, M. et al., J. Clin. Immunol. 5:272-2 (1978); Dill, H. et al., Int. J. Clin. Pharmacol. Biopharm. 15:17-18 (1977)), and peroxydiphosphate (Afflitto, J. et al., J. Dent. Res. 67(Spec. Iss. March):401 (1988); Coleman, E.J. et. al., J. Dent. Res 67(Spec. Iss. March):296 (1988); Nabi. N. et al., J. Dent. Res. 67(S Iss. March):151 (1988)).

The compilation of the components of the aforementioned oral composi is based upon the specific properties of each of the individual components, wherein each component of the combination increases the anti-plaque effectiveness of other members of the combination.

The oral composition of the invention assists in the prevention of d caries and periodontal disease, and in the relief of symptoms result from existing gingival and subgingival problems, by attacking the pathogenic bacteria responsible for plaque formation and consequent cariotic and periodontal diseases.

The composition effective for the treatment or prevention of plaque, dental caries or periodontal disease is such that the antibacterial can be released in a sustained, long-term fashion, and such that the antibacterial composition has the property of long-term adhesion to gums and teeth, and such that the antibacterial composition remains plastic during the entire period of application.

It is also a feature of this invention that the aforementioned bacteriocidal anti-plaque agent is released to the sites of carious lesions and periodontal pockets in a long-term sustained release man as to reduce the required frequency of use.

The compositions of the invention are especially useful in the treat of gingivitis in animals, and especially pets. The major cause of de the U.S. of dogs and cats over four years old is starvation due to t loss. The composition of the invention may be formulated to contain anti-bacterial agent, and preferably chlorhexidine, and applied to t teeth of animals with an applicator, so as to help treat or prevent against gingivitis-induced tooth loss.

2. Tooth Hypersensitivity

As indicated above, a variety of anti-hypersensitivity agents are su for the present invention. Preferred is the use of strontium salts. anti-hypersensitivity agents useful in the composition of the invent include potassium, lithium or sodium nitrate, potassium bicarbonate, potassium chloride, hydroxyapatite, fluorapatite, ammonium oxalate, with fluoride, fluoride, and ammonium glycyrrhizzinate. In a composi effective for the treatment or prevention of tooth hypersensitivity, active anti-hypersensitivity agent is released in a sustained, long- fashion, without a salty or metallic taste. The hypersensitivity composition has the property of long-term adhesion to the teeth, and able to remain plastic during the entire period of application.

3. Oral Candidiasis and Other Oral Fungal Infections

The liquid polymer composition of the present invention may be emplo the treatment or prevention of oral candidiasis as well as other ora fungal diseases. The oral composition of the invention assists in th prevention of microfungal infections of the oral cavity and periodon tissue, and in the relief of symptoms resulting from existing microfungally-caused problems, by attacking the pathogenic yeast and responsible for the infection in the oral cavity. As indicated above variety of antifungal agents are suitable for the present invention. addition to the treatment and prevention of oral infections, the liq polymer compositions of the present invention may be used to treat f infections which affect other mucosal tissue. For example, the liqui polymer composition of the present invention may be used in the trea of yeast, chlamydial, etc. infections of the vagina.

In another embodiment, combinations of more than one antifungal agen used in the composition of the invention. Combinations of antifungal agents can for the purpose of providing treatment or protection agai broad spectrum of microfungal species, or for the purpose of attacki specific microfungal species with drugs acting through different mod action. Combination of antifungal agents may also allow a lower dose given antifungal agent to synergistically act with a lower dose of a antifungal agent in a manner which is efficacious in combination but separately.

The antimycotic composition may be formulated to include other drugs as antibacterial or antiseptic agents also known to the art.

One feature of this invention is that the aforementioned antifungal is released to the sites of fungal lesions and pockets in a long-ter sustained release manner so as to reduce the required frequency of u Long-term sustained release is desirable because it improves patient compliance with the treatment protocol and it is more convenient for patient. Hence the success of the treatment is more probable. The me of the invention needs only a single or few applications of the liqu polymer composition to remain efficacious for a period of weeks. Oth methods require a multi-dose application of paste every few days or ingestion of lozenges every four hours by the patient. At best, the remain effective for 2-3 days and the lozenges only for hours.

In addition, by the composition and method of the invention, because the long-term sustained release of the drug, much lower amounts of t antifungal drug are required for efficacious results. Conventional t uses doses of nystatin as high as 10.sup.8 IU/dose. In contrast, substantially lower doses are efficacious when used in the liquid po compositions of the present invention. Because of the lower doses of nystatin, the side effects of the drug are eliminated or minimized. example, at the efficacious concentrations of nystatin taught by the compositions and methods of the invention, the bitter taste associat with nystatin is found to be substantially less objectionable. The b taste of the drug is one of the major complaints of patients taking conventional nystatin therapy.

Moreover, the physical form and manner of presentation of the compos of the invention is highly advantageous for a patient with an oral microfungal infection. Often the area of the infection is so sore so make the direct application of a paste or even sucking lozenges, tro or pastilles very painful; rinsing with a mouthwash does not leave

efficacious levels of the drug in the oral cavity. In other cases, o treatments with mouthwashes, lozenges, pastes, troches or pastilles very difficult or just not practical, for example with infants or an The compositions and methods of the invention solve this problem by applying the antifungal drug to the teeth or other orthodontic appar for slow, long-term sustained release at efficacious levels into the salival fluids of the oral cavity.

4. Sterilization of Root Canals

In addition to the above-described uses, the liquid polymer composit of the present invention can be employed as a means of sterilization root canal procedures. For such treatment, the composition would preferably include an antiseptic agent (most preferably camphorated parachlorophenol (CPK). Use of the composition of the invention with provides a highly-desired prolonged period of effectiveness for such treatment. For example, in the typical procedure wherein CPK is curr used to sterilize root canals, a paper point is dipped into CPK and inserted into the root canal which is then closed with a temporary filling. The anti-bacterial agent in that case is only effective for hours. However, utilizing the composition and method of the inventio wherein the liquid polymer is used as a matrix for CPK, the anti-bac agent is released in an active form for a period of 3-4 days, thus m the sterilization process more effective.

Further, it is possible to design a degradable polymer system simply replacing EUDRAGIT S (polymer type B) with EUDRAGIT L (polymer type and injecting the liquid into the root canal.

5. Other Oral/Dental Uses

The compositions can also be used to treat or prevent infection in t socket of an excised wisdom tooth, or in a gingival abscess. The liq polymer can be injected directly into the periodontal pocket, formin film in situ and releases the active material in a controlled manner a desired period of time. As described herein, the compositions of t invention may be formulated so that, simultaneous with the controlled-release, the film disintegrates. By injecting the liquid polymer in this way, the film forms in the shape of the pocket and t amount of liquid polymer needed can be determined by the pocket size Thus, there is no need for predetermination of the amount to be administered as there is with a "chip." Also, this liquid polymer is especially appropriate to use with small pockets (those less than 4 depth), rather than creating a smaller chip especially sized for the area. For this purpose, the composition would contain an antiseptic, antibacterial, an anti-inflammatory agent, an analgesic, and/or an antifungal agent (chlorhexidine digluconate is the preferred agent).

The invention also provides an absorbent point, gauze, or film in combination with a controlled-release composition containing a liqui polymer and an active agent, especially CPK.

The compositions may also be adapted to treat denture stomatitis (Arendorf, T.M. et al., J. Oral Rehabil. 14:217-227 (1987); Stohler, Schweiz Monatsschr Zahnmed, 94:187-194 (1984), which references are incorporated herein by reference), by containing an anti-fungal agen (most preferably nystatin). The compositions can be adapted to treat

aphthous ulcers (Brazelton, F., GMDA Bull 50:219-220 (1983); Chawda, et al., Ann. Dent:43:14-17 (1984), which references are incorporated herein by reference), canker sores, or burns (as from food such as p molten cheese, etc.) by the inclusion of saccharin and ethyl alcohol and/or cetylpyridinium chloride. Chlorhexidine gluconate may alterna be employed for this purpose (mouthrinses containing chlorhexidine gluconate have been used to treat candida infections as reported by M. et al. in J. Clin. Periodont. 14:267-273 (1987), which reference incorporated herein by reference).

The composition of the invention, because of its ability to adher to and to deliver agents for the treatment of pain and inflammation, ma be used to treat teething pain in children.

The composition of the invention can also be used for dental estheti for example, tooth whitening. Such whitening can be performed by usi composition of the invention to continuously deliver low levels of a bleaching or oxidizing agent directly to the enamel surface of the t crown. Examples of such oxidizing and bleaching agents include chlor peroxide, hydrogen peroxide and urea peroxide. Use of the compositio the invention for such purposes is more efficient and exposes the pa to fewer toxic risks than present methods.

In a manner analogous to the treatment of oral fungus conditions, th compositions of the invention may also be used to deliver efficaciou levels of an anti-tumor agent to a tumor in the oral cavity. Such compositions may be applied as a varnish directly to the tumor and/o applied at a location wherein efficacious levels of the anti-tumor a are released into the milieu surrounding the tumor. If desired, mult coatings of films may be used. For example, a first layer of the anti-tumor-containing composition may be applied directly upon the s the tumor, so that a film is formed over the site of the tumor, and first layer then coated with a second layer which provides propertie different from those of the first layer. For example, the second lay be impermeable to the anti-tumor agent so as to only permit delivery the anti-tumor agent from the side of the film which faces the tumor the second layer may provide a second active agent and/or provide fo rate of release of an active agent which is different from that of t first layer.

B. Dermatological Uses

The liquid polymer compositions of the present invention may be empo in the treatment or prevention of dermatological diseases or conditi As used herein, a dermatological disease or condition is one which a the skin. In one embodiment, the liquid polymer composition may be a directly to the skin surface. Alternatively, the composition may be applied to a bandage, dressing, etc. and then placed in contact with affected skin surface.

The liquid polymer of the invention can be used for the delivery of growth factors and tissue growth factors or alternatively to provide occlusive membrane over damaged bone and/or tissue, thus enhancing t regenerative response.

Examples of dermatological diseases and conditions which may be trea prevented by use of the present invention includes acne vulgaris, in

bites, impetigo, burns, ringworm, tinea versicolor, cutaneous candid molluscum contagiosum, sunburn, allergic contact dermatitis (such as reaction to poison ivy, poison oak, bee venom, etc.), exfoliative dermatitis, eczematous dermatitis, warts, herpes simplex or zoster lesions, chicken pox lesions, rubella macules or papules, pustules, psoriasis, Lyme disease lesions, general inflammatory responses (i.e rashes, etc.), urticaria, erythema multiforme syndrome, purpura, ski tumors, etc. Further examples of dermatological diseases or conditio which may be treated or prevented using the liquid polymer compositi the invention are disclosed in Harrison's Principles of Internal Med 11th Edition, Braunwald, E. et al. (eds.), McGraw-Hill, N.Y. (1987), reference is incorporated herein by reference). The liquid polymer compositions of the present invention can be employed in the treatme cuts, bruises, and the like, to prevent subsequent bacterial, fungal viral infection.

The compositions of the present invention are especially well suited dermal application since thereby are resistant to abrasion and remov water or perspiration. Such concerns are especially significant in compositions for the treatment of burns, bruises, and sunburn. The w resistant nature of the films formed from the drying of the liquid p compositions of the present invention makes such liquid polymer compositions especially suitable for use in the treatment or prevent sunburn.

Although the foregoing has exemplified the dermatological uses of th invention, it will be understood that the liquid polymer composition the present invention may be used in the topical treatment of any mu surface. Thus, for example, liquid polymer compositions which contai antibiotics or anti-viral agents may be applied to the vagina or pen the treatment of venereal disease (such as gonorrhea, syphilis, herp infections, etc.).

In addition to the aforementioned uses, the liquid polymer compositi the present invention may be used in cosmetics (as by formulating th contain moisturizing agents, retinoid A (or other anti-wrinkle agent etc.).

Having now generally described the invention, the same will become b understood by reference to certain specific examples which are inclu herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

EXAMPLE 1

Since toothbrushing generally proves to be sufficient in preventing plaque, the use of chemicals which reduce plaque and could be delive forms likely to be widely accepted by the general public have been assiduously sought by dental scientists. Many quaternary ammonium sa the form of mouthwashes, dentifrice, solutions and gels have proven successful in preventing periodontal diseases. Among them, chlorhexi and cetylpyridinium chloride (CPC) are the most effective against pl

Sustained release drug treatment is expected to be efficacious in lo and prolonged action rather than the conventional antibacterial ther (mouthrinse and dentifrice). Thus, a CPC liquid polymer solution whi be spread on the teeth to form a drug-containing film is desirable.

drug is expected to be released into the mouth cavity and into plaqu substance which accumulates on teeth. The release should be terminat after a night's sleep (average: 5-6 hours), while at the same time, film degrades.

In an attempt to assess the in vitro release of CPC from liquid poly films composed of acrylic polymers, a broad series of experiments we performed in which different polymers and plasticizers and several additives were formulated and tested.

1. Liquid polymer Preparation--General Description

The formulations were all prepared by the same general procedure, described as follows: the polymer (EUDRAGIT.RTM., Roehm Pharma Gmbh, Darmstadt, W. Germany), polyethylen glycol (PEG), and the CPC were dissolved in ethanol. After complete dissolution of these ingredient additional components in aqueous solution were added, while continuo stirring. The ratio of film components to solvents (water/alcohol) w 1:3.

2. In-vitro evaluation

Liquid polymer solutions containing the requisite weights of CPC and polymer were poured on Teflon plates. The films were generated after allowing the solvent to evaporate for 12-15 hours at room temperatur films (containing 1-5% water) were cut to rectangular forms of 1.tim cm in an area and accurately weighed. The films were then placed in containing 5 ml phosphate buffer (0.02 M, pH 6.8) previously warmed 37.degree. C. and incubated for 6 hours. Samples were taken at time intervals of 5, 15, 30, 60, 90, 210, 270, 330, and 360 minutes. The concentration of CPC released was determined by UV spectrophotometer (UVIKON 930, Kontron Instruments) at 254 nm against standard calibra curve.

In these experiments, EUDISPERT mv or EUDRAGIT L was added to the formulations containing CPC and EUDRAGIT RL. EUDISPERT mv and EUDRAG are relatively water-soluble polymers. Table I shows the weight perc components in films prepared from 5 liquid polymer compositions (i.e MM42, MM43, MM44, MM47, and MM48). The liquid compositions were drie the cumulative percentage of released CPC was determined. FIG. 1 sho cumulative release percentage of CPC from the films produced by the of the 5 liquid polymer compositions.

TABLE I Weight percent of components in film formulations

Exp. No.	MM42	MM43	MM44	MM47	MM48
CPC	30	30	30	30	30
EUDRAGIT RL	32.5	30	40	55	
PEG 400	25	25	25	--	--
EUDRAGIT L	--	--	--	30	--
EUDISPERT mv	10	12.5	15	--	15

EXAMPLE 2

In these experiments EUDISPERT mv or EUDRAGIT L were added to formul containing a combination of 50:50 EUDRAGIT RL/EUDRAGIT RS either wit 400 or without it. Table II shows the weight percent of components i films prepared from 4 liquid polymer compositions (i.e. MM50, MM51, and MM53). The liquid compositions were dried, and the cumulative percentage of released CPC was determined. FIG. 2 shows the cumulati

release percentage of CPC from the films produced by the drying of t liquid polymer compositions.

TABLE II Weight percent of components in film formulations Exp. No. MM50 MM51 MM52 MM53 CPC 30 30 30 30 EUDRAGIT RL 1 20 30 EUDRAGIT RS 15 25 20 30 PEG 400 10 10 20 30 EUDRAGIT L 30 -- 3 EUDISPERT mv -- 10 -- 10

EXAMPLE 3

This example involved various Eduispert mv concentrations in formula containing CPC, EUDRAGIT L and PEG 400. Table III shows the weight p of components in films prepared from 7 liquid polymer compositions (MM35, MM36, MM37, MM38, MM39, MM40 and MM41). The liquid composition dried, and the cumulative percentage of released CPC was determined. 3 shows the cumulative release percentage of CPC from the films prod by the drying of the 7 liquid polymer compositions.

TABLE III

Exp. No.	MM35	MM36	MM37	MM38	MM39	MM40	MM41
CPC	30	30	30	30	30	30	30
EUDRAGIT L	45	42.5	40	37.5	35	32.5	30
PEG 4	25	25	25	25	25	25	25
EUDISPERT mv	--	2.5	5	7.5	10	12.5	15

EXAMPLE 4

CPC and EUDRAGIT L preparations were made containing various PEG 400 concentrations. Table IV shows the weight percent of components in f prepared from 5 liquid polymer compositions (i.e. MM30, MM67, MM68, and MM35). The liquid compositions were dried, and the cumulative percentage of released CPC was determined. FIG. 4 shows the cumulati release percentage of CPC from the films produced by the drying of t liquid polymer compositions.

TABLE IV Exp. No. MM30 MM67 M MM46 MM35 CPC 30 30 30 30 30 EUDRAGIT L 70 65 60 55 45 PEG 400 -- 5 10 15 25

EXAMPLE 5

These experiments included an addition of various concentrations of acid as release enhancers. Table V shows the weight percent of compo in films prepared from 4 liquid polymer compositions (i.e. MM30, MM2 MM31, and MM32). The liquid compositions were dried, and the cumulat percentage of released CPC was determined. FIG. 5 shows the cumulati release percentage of CPC from the films produced by the drying of t liquid polymer compositions.

TABLE V Exp. No. MM30 MM28 MM MM32 CPC 30 30 30 30 EUDRAGIT 60 65 67.5 CITRIC ACID -- 10 5 2.5

EXAMPLE 6

Two formulations containing 0.3% lysine (in film), EUDRAGIT L, and C were prepared. Only one was prepared with PEG 400. The ability of th preparations to mediate drug release was determined. Table VI shows weight percent of components in films prepared from 2 liquid polymer compositions (i.e. MM57 and MM59). The liquid compositions were drie the cumulative percentage of released CPC was determined. FIG. 6 sho cumulative release percentage of CPC from the films produced by the of the 4 liquid polymer compositions.

TABLE VI

Exp. No.	MM57	MM59
CPC	30	30
EUDRAGIT L-100	54.7	
LYSINE HCl	0.3	0.3
PEG 400	15	--

These formulations were prepared with 0.5% lysine (in film) EUDRAGIT CPC and various concentrations of PEG 400. Table VII shows the weigh percent of components in films prepared from 4 liquid polymer compos (i.e. MM60, MM65, MM66, and MM58). The liquid compositions were drie the cumulative percentage of released CPC was determined. FIG. 7 sho cumulative release percentage of CPC from the films produced by the of the 4 liquid polymer compositions.

TABLE VII

Exp. No.	MM60	MM65	MM58
CPC	30	30	30
EUDRAGIT	69.5	64.5	59.5
LYSINE HCl	0.5	0.5	0.5
PEG 400	--	5	10

EXAMPLE 8

Formulations were prepared with 1% of lysine (in film), EUDRAGIT L, and various concentrations of PEG 400. Table VIII shows the weight p of components in films prepared from 5 liquid polymer compositions (MM54, MM61, MM62, MM63 and MM64). The liquid compositions were dried the cumulative percentage of released CPC was determined. FIG. 8 sho cumulative release percentage of CPC from the films produced by the of the 5 liquid polymer compositions.

TABLE VIII

Exp. No.	MM54	MM61	MM63	MM64
CPC	30	30	30	30
EUDRAGIT L	69	64	59	54
LYSINE HCl	1	1	1	1
PEG 400	--	5	10	15

EXAMPLE 9

In these experiments, no PEG was included. They were prepared with C EUDRAGIT L and various concentrations of lysine. Table IX shows the percent of components in films prepared from 6 liquid polymer compos (i.e. MM30, Mm60, Mm54, MM55, Mm56 and MM49). The liquid composition dried, and the cumulative percentage of released CPC was determined. 9 shows the cumulative release percentage of CPC from the films prod by the drying of the 6 liquid polymer compositions.

TABLE IX

Exp. No.	MM30	MM60	M
CPC	30	30	3
EUDRAGIT	70	69.5	69
LYSINE	--	0.5	1
HCl			

EXAMPLE 10

Formulations were prepared containing 15% PEG 400 (in film). They we prepared with CPC, EUDRAGIT L, PEG 400 and various concentrations of lysine. Table X shows the weight percent of components in films prep from 4 liquid polymer compositions (i.e. MM46, MM57, MM58, and MM63) liquid compositions were dried, and the cumulative percentage of rel CPC was determined. FIG. 10 shows the cumulative release percentage from the films produced by the drying of the 4 liquid polymer compositions.

TABLE X

Exp. No.	MM46	MM57	MM63
CPC	30	30	30
EUDRAGIT L 60	59	54.7	54.5
PEG 400	10	10	10
LYSINE HCl	--	0.5	1

EXAMPLE 11

Formulations were prepared containing 10% PEG 400 (in film). They we prepared with CPC, EUDRAGIT L, PEG 400 and various concentrations of lysine. Table XI shows the weight percent of components in films pre from 3 liquid polymer compositions (i.e. MM68, MM66, and MM62). The compositions were dried, and the cumulative percentage of released C determined. FIG. 11 shows the cumulative release percentage of CPC f the films produced by the drying of the 3 liquid polymer composition

TABLE XI

Exp. No.	MM68	MM66	M
CPC	30	30	30
EUDRAGIT L 60	59	54	54
PEG 400	10	10	10
LYSINE HCl	--	0.5	1

EXAMPLE 12

A summary of formulations containing various amounts of PEG 400 and with their degradation times in buffer solution (0.02M, pH 6.8) was determined. Table XII shows the affect on degradation caused by alte the percent PEG 400 and % lysine components in films prepared from 1 liquid polymer compositions. The liquid compositions were dried, and time of disappearance of the film was determined.

TABLE XII

Exp. No.	% PEG	% ly	Time of disappearance
A. MM35	90	MM46	15 -- 270
MM66	10	--	300
MM67	5	--	330
MM30	--	--	>360
B. MM	1	150	MM63 15 1 210
MM62	10	1	330
MM61	5	1	>360
MM54	--	1	>360
C. MM	0.5	210	MM66 10 0.5 330
MM65	5	0.5	>360
MM60	--	0.5	>360

EXAMPLE 13

Sustained release of CPC from film matrices was achieved with an arr formulations possessing a broad range of kinetic profiles (FIGS. 1-1 Films which were prepared with EUDRAGIT RL/RS were not homogeneously formed unless EUDISPERT mv was added. Moreover, by incorporating EUD polymer in the matrices, a partially degradable film could be achiev however, these films released the drug within 15-20 minutes and a pl was then observed.

FIG. 1 shows a drastic decrease in the total amount of drug released (after the short burst) when EUDISPERT concentrations increase by sm increments (10%, 12.5%, and 15%). This exhibits a possible interacti between drug, EUDISPERT and EUDRAGIT RL polymers, or a presence of s sort of cross-linking which can form between the polymeric chains, resulting in drug trapping in the matrix. The use of EUDRAGIT L, whi contains lower molar concentration of carboxylic acid groups than EUDISPERT, thoroughly changes the release profile of CPC (see FIGS. 2).

By adding PEG 400 to the formulations (MM50 and MM51), the differenc the release patterns were significantly diminished (FIG. 2). Films w were prepared with EUDRAGIT L were quite different in their features 4 shows the release of CPC from EUDRAGIT L films containing elevatin concentrations of PEG. In addition to the influence of PEG on the re kinetics, the disintegration time was also dependant upon its concentration as can be seen in Table XII-A. In comparison, citric a changes the release kinetics (FIG. 5), but does not affect the solub or the degradability of the films.

FIGS. 6-10 demonstrate the contribution of lysine hydrochloride to t release of CPC from EUDRAGIT L films. When no PEG was used in the formulations (FIG. 9), the addition of 0.5 to 5% of lysine significa increased the rate of CPC release, but no substantive difference bet the various lysine concentrations was observed. When 15% PEG 400 was to the formulations (see FIG. 10), the rate of CPC release was also increased with the rise of lysine content from 0.5% and above. No significant change in the release kinetics was noticed in a formulat containing 0.3 of lysine. In contrast to this phenomenon, the additi 10% PEG or less did not increase the release rate but significantly changed the kinetic profile of CPC release. As can be seen in FIG. 1 addition of 0.5% and 1% lysine smoothed the curve and formed a const rate of release.

The disintegration rate of CPC-EUDRAGIT L films is also affected by lysine, as is indicated in Table XII. The addition of 0.5% or 1% lys hydrochloride to the film increased the time taken for the film to disappear by approximately 30 minutes (300 to 330 minutes and 330 to 360 minutes). There was one exception in a formulation which contain PEG, where a decrease in time was observed (270 to 210 minutes). Thi exception might correspond to the abovementioned phenomenon of diffe release kinetics between formulations containing 15% PEG and various lysine concentrations and formulations with 10% PEG and less. It is postulated that two ion-exchange mechanisms of lysine action exist i order to explain the different release patterns: 1. a delay in the p solubilization by cross-linking interaction, and 2. a competition of lysine with the quaternary ammonium drug on the polymer's active sit

For anti-plaque compositions, EUDRAGIT L and RL are the preferred polymers. EUDRAGIT L is the most preferred polymer for an anti-plaqu composition. EUDRAGIT L was found appropriate for the preferred mode application. If forms a homogeneous film which can disintegrate in a hours, releasing CPC in a sustained manner. The use of PEG, citric a and lysine hydrochloride aid in controlling the release of the drug. and probably citric acid as well, acts as a plasticizer within the polymeric matrix. These agents act to reduce crystallinity and incre

the accessibility to water diffusion. Citric acid, which contains th carboxylic acid salts, can act also as a drug carrier by interact wi CPC's quaternary ammonium group. This interaction, which results in soluble complex, actually competes with a similar interaction involv the polymer and the drug. The latter interaction, however, does not in a soluble complex and it actually causes a delay in the drug rele

Lysine, in contrast, has the ability to form cross-linking bonds bet the polymer backbone chains and delay the release by reducing the polymer's permeability. In fact we found the opposite, when the rele rate increased with elevation of lysine concentrations (see FIGS. 9, This suggests that the cross-linking mechanism is not as dominant as another mechanism of action involving interference of drug-polymer interaction by competing on the polymer's active sites. Nevertheless cross-linking mechanism is postulated to occur when relatively low concentrations of PEG (10% and less) are used, forming an appropriat space for the cross interaction. As has already been noted above, th delay in the disappearance of the films which contain 10% or 5% PEG indicate cross-linking rather than a competition mechanism.

The preferred anti-plaque composition of the present invention is formulation MM66 (FIG. 7, Table VII). This preparation contains 30% 0.5% lysine hydrochloride, 10% PEG, and 59.5% EUDRAGIT L in the drie film.

There are two advantages in using this liquid polymer preparation:

1. It releases the drug at a constant rate and in a prolonged manner

2. It degrades or disintegrates completely (in buffer solutions) aft hours, which corresponds to overnight application.

EXAMPLE 14

Hypersensitivity of the teeth to heat, cold, sweet food or mechanica stimulation is caused by decay of the enamel or gum recession. Expos the dentin results in increased movement of calcium in the ion chann which in turn causes painful stimulation of the nerve endings.

Strontium chloride has been shown to be effective in the treatment o hypersensitive teeth. It is believed to act either by entering the c channels and displacing calcium at the nerve endings, or by blocking channels at the dentin surface by deposition as insoluble salts. Sen toothpaste has strontium chloride as the active ingredient. Its effectiveness is limited, however, by its very short contact time, t toothpaste being washed away after a minute or two.

To overcome this limitation, a sustained-release formulation has bee developed for strontium chloride by incorporating it into a biodegra acrylic polymer. The polymer, dissolved in aqueous alcohol, is prefe "painted" on the teeth (as by soft brush, spray, etc.) to form a qui drying film or liquid polymer. Preferably the film will release its strontium steadily over a few hours and will itself be slowly degrad overnight. The patient will thus be able to apply the film in the ev before going to sleep and by morning it will have disappeared.

Formulation of Films

Formulations were prepared in 70% alcohol by the dissolution of EUDR and PEG 400 (where applicable) in alcohol followed by the slow addit aqueous solutions of strontium chloride and other salts (as applicab the stirred mixture. 70% alcohol was chosen as the best balance betw the conflicting requirements of a film that is quick-drying but does cause undue pain upon oral application. The ratio of total film comp to total solvents in the formulations was in the range of 1:3 to 1:4 (w/v), an alcoholic polymer solution of the highest workable viscosi (c.a. 0.33 g/ml) being used every time. High concentration is a nece requirement for a quick-drying film that can be spread or painted on teeth, but if too viscous, the components cannot be mixed in well. Formulations containing trisodium citrate were white suspensions and without this salt were opaque solutions.

Films were prepared by spreading each formulation over a 6.5 cm diam teflon dish and allowing to dry overnight at room temperature. The u a weight of formulation calculated to produce approximately 0.5 g of film resulted in films with a mean thickness of 194.mu. (standard deviation 34.mu.).

In Vitro Release

The release of strontium from films in the mouth was simulated in vi 1.5-cm square (34-44 mg) was cut and placed in 3 ml of pH 6.8 phosph buffer (0.04M) in a thermostatically controlled water bath at 37.deg C. with gentle shaking. At suitable intervals until the film had tot dissolved, the film was transferred to a fresh vial containing anoth ml of buffer. This crudely simulated the continuous renewal of saliv the mouth and also enabled the amount of strontium released at each interval to be measured. The film was also weighed at hourly interva obtain an indication of its disintegration profile. More frequent weighings were precluded by the need to dry the film in air for at l minutes before weighing.

Release of strontium and disintegration of the film are expected to slower in vivo than in this model because of the very limited moveme saliva in the mouth during sleep. We therefore aimed for a film that release strontium steadily over 1-2 hours and disintegrate in 2-4 ho under these experimental conditions.

Analysis for Strontium

The samples of buffer from the release experiments were analyzed for strontium content by atomic absorption with an air-acetylene flame a detection of the 460.7 nm line. Standard solutions of strontium chlo in the buffer were used to construct a calibration curve, which was to be linear in the range of 0.5-8 .mu.g/ml of strontium, and the sa were further diluted in the release buffer accordingly. From the wei of wet formulation on the plate, dry film, and film square, the weig strontium in the film square could be calculated, and thus the concentrations of strontium in the samples were translated into perc strontium released. As the total calculated recovery of strontium fr films generally differed somewhat from 100%, the results were normal to 100% total release, the films having been totally degraded.

To ensure that no other component of the films absorbed at the stron

absorption wavelength, a number of blank formulations without stront were prepared in parallel with the strontium formulations and films made in an identical manner. Then for the in vitro release experimen parallel experiments on squares of the blank films were carried out well and the samples read by atomic absorption after dilutions simil those of the positive samples. The readings were zero in every insta and after a number of such experiments, the preparation of blank fil discontinued.

EXAMPLE 15

The strontium-release and degradation profiles for the array of formulations tested are shown graphically in FIGS. 12-18. Accompanyi each figure or pair of figures is a table (below) detailing the composition of the relevant films, expressed as weight percent of th components. It should be noted that these values include water of crystallization of hydrated salts, which was found to be retained in fried films. In fact, the films contained 0-10% additional entrapped water, as revealed by their dry weights which were generally slightl higher than calculated from the weights of the components. This addi water has not been taken into account for the composition data.

Films containing only the polymer, strontium chloride and various concentrations of PEG 400 released 50-70% of the strontium in the fi minutes (FIG. 12) while it took between 1.5 and 4 hours for the film be totally degraded (FIG. 13). The composition of these films is sho Table XIII.

TABLE XIII Weight % of Compon of Film Component D4A D13 D8B D7D Strontium Chloride 10 10 10 10 Hexahydrate EUDRAGIT L 65 78 85 90 PE 25 12 5 -- Trisodium Citrate -- -- -- -- Dihydrate Calcium Chloride -- -- Dihydrate

The different time scales of the two graphs should be noted. The rat both strontium release and degradation increase with increasing concentrations of the plasticizer.

The addition of 7.4% trisodium citrate to the films dramatically red the rate of strontium release (FIG. 14). The composition of these fi shown in Table XIV.

TABLE XIV Weight % of Compone Film Component D6C D9C Stront Chloride 10 10 Hexahydrate EUDRAGIT L 57.6 82.6 PEG 400 25 -- Trisod Citrate 7.4 7.4 Dihydrate Calcium Chloride -- -- Dihydrate

Almost linear, zero-order kinetics prevail with only 13-19% release first 15 minutes. FIG. 14 also illustrates the range of results from replicate in vitro release experiments. Both replicate squares from same film and squares from replicate films were tested, and replicat were neither prepared nor tested on the same day.

FIG. 15 highlights the effect of the addition of trisodium citrate a also shows that the inclusion of PEG increased the rate of strontium release from citrate-containing films as it did for films without ci

The degradation rate was similarly increased by PEG (FIG. 16), but appeared to be unaffected by trisodium citrate. The composition of t films is shown in Table XV.

TABLE XV Weight % of Componen

Film Component	D4A	D7D	D6C	D9C
Strontium Chloride Hexahydrate	10	10	10	10
EUDRAGIT L	65	90	57.6	82.
400	25	--	25	--
Trisodium Citrate Dihydrate	--	--	7.4	7.4
Calcium Ch	--	--	--	--

The symmetry between the release and degradation profiles of films w trisodium citrate (FIG. 16) indicates that the strontium was release steadily over the entire period of degradation of these films, quite different from the behavior of films without citrate (FIGS. 12 and 1

When the concentration of trisodium citrate in the film was reduced half, a strontium release profile of intermediate rate was obtained 17). The opposite effect was displayed by a formulation containing c chloride in addition to trisodium citrate. The initial release rate even faster than films without additives, reaching 60% in the first minutes (FIG. 18). No effect on the degradation profile was observed either additive. The composition of these films is shown in Table XV

TABLE XVI Weight % of Compone

Film Component	D7D	D14av	D9C	D15av
Strontium Chloride Hexahydrate	10	10	10	10
EUDRAGIT L	90	86.3	82.6	7
PEG 400	--	--	--	--
Trisodium Citrate Dihydrate	--	3.7	7.4	7.4
Calci				
Chloride Dihydrate	--	--	--	2.8

EXAMPLE 16

The introduction of strontium chloride into a matrix of EUDRAGIT L w additives imparts a limited measure of sustained release. Initial re is rapid, however, and appears to be diffusion controlled, being muc faster than the dissolution of the polymer. This increased rates of release and degradation when polyethylene glycol is added to the formulation are possibly due to its action as a plasticizer, increas the separation between layers of the polymer and thus allowing easie penetration of the buffer.

A different mechanism may be responsible for the zero order release kinetics observed in the presence of 7.4% trisodium citrate. At this concentration the divalent strontium ions in the formulation are exa balanced by two equivalents of carboxyl groups, and indeed, the appe of a voluminous precipitate in the formulation on addition of the ci implicates the formation of strontium citrate (or more precisely tristrontium dicitrate), which is only slightly soluble. Being a lar molecule than strontium chloride, strontium citrate may be effective entrapped within the polymer and its low solubility may further limi ability to diffuse out until the polymer surrounding it dissolves. A alternative explanation is that the divalent strontium ions are link one side to citrate carboxyl groups and on the other side to carboxy groups of the polymer and as such can only enter solution together w the polymer.

The difference between the mechanisms of strontium release with and without sodium citrate was further highlighted by in vitro release

experiments done in pure water, which does not dissolve the polymer. Without sodium citrate a release profile similar to that in buffer w observed. In the presence of sodium citrate, however, 12% of the str in the film square was released within the first half hour and only further 1% subsequently; the remaining 87% was not released at all. small proportion released was either non-entrapped strontium on the surface of the film of free strontium not bound to the polymer. Henc rates of release and degradation of films containing 7.4% sodium cit may be similar (FIG. 16) because the former is dependent on the latt is controlled by it.

If strontium is bound to the polymer in the film, the possibility wa considered that it remains bound after dissolution of the polymer an such would not be effective for the treatment of hypersensitive teet This was discounted by dialysis of dissolved citrate-containing film against the same buffer. After 48 hours and one change of buffer, at absorption revealed only 0.1% of the strontium remaining in the poly solutions. Thus even if the strontium is bound to the polymer in the film, it is released as free ionic strontium and ought to be therapeutically effective.

The addition of 2.8% calcium chloride, half the molar quantity of th strontium chloride, to citrate-containing films was expected to incr the release rate by competition with strontium for the available cit giving a release profile similar to that from the film with half the quantity of sodium citrate (FIG. 17). The result, however, was surpr (FIG. 18). Calcium appears to expel strontium from citrate-containin films at a rate faster even than the release of strontium from films containing no citrate or calcium.

In conclusion, the film D9 (containing strontium chloride hexahydrat EUDRAGIT L, and trisodium citrate dehydrate) is the preferred anti-hypersensitivity composition of the present invention, releasin strontium and being degraded steadily over 3-4 hours. Although this formulation contains a precipitate, it settles only slightly over a of a few days. If a slightly faster initial release is desired, the of trisodium citrate can be reduced (as in film D14), or if the degradation in vivo is found to be too prolonged, polyethylene glyco be added (as in film D6). The precipitates in D6 and D14 settled wit one day, but it should be possible to prolong settling by an increas the viscosity of the formulation (reduction of the solvent volume) o the addition of a suitable detergent.

EXAMPLE 17

Potassium ion has been used in a variety of dentifrice formulations designated to treat dentin hypersensitivity. The compositions of two anti-hypersensitivity compositions are shown in Table XVII. Composit contains a plasticizer which also acts as an ionic surfactant formin homogeneous potassium phase. Composition 2 contains an ion-pair agen which is a relatively water insoluble substance.

TABLE XVII

	Composition (% w/w
	Potassium Chloride 2.25 --
Potassium Hydrogen Tartrate -- 4.5 Methacrylic acid copolymer 18.02	
Sodium docusate 2.25 -- Alcohol 50.45 50.45 Water 27.03 27.03	

EXAMPLE 18

The ability of the anti-plaque liquid polymer of the present inventi prevent or attenuate the accumulation of plaque on tooth surfaces wa evaluated using 50 human volunteers. The teeth of the volunteers wer cleaned (by scaling) to remove accumulated plaque. The volunteers we then divided into two groups. One group received daily treatment wit formula MM66 CPC-containing, anti-plaque liquid polymer (discussed i Example 13); the other group received daily treatment with a placebo various times after the scaling, the teeth of the volunteers were ex and the plaque indices (PI) of the tooth surface were ascertained. A PI value indicates less plaque accumulation than a higher PI value. results of this experiment are shown in Table XVIII.

TABLE XVIII _____ Percent of Tooth Surface.sup.1 Scored as: Time in PI = 0 PI = 3 Days Active Placebo A Placebo _____ 0.sup.2 12.1 10.6 31. 8 38.7 27.0 6.8 6.4 22 45.2 22.2 11.4 17.6 26 49.3 32.1 6.2 13.1 _____ .sup.1 Distal, mesial, buccal lingual, and palatial surfaces on the anterior teeth were scored. .s Day of scaling; PI determined prior to scaling

EXAMPLE 19

Formulations of liquid polymer compositions were prepared for variou uses. The formulations are the preferred compositions for the respec uses. Values are presented in percent weight by weight (% w/w).

_____ A. LIQUID POLYMER COMPOSITION DENTURE STOMATITIS Methacrylic acid copolymer type A 10.0 Methacryli copolymer type A 9.0 Nystatin 2.4 Polyethylene glycol 400 2.4 Ethyl alcohol 76.2 B. LIQUID POLYMER COMPOSITION FOR ORAL CANDIDIASIS Methacrylic acid copolymer type A 19.0 Polyethylene glycol 400 2.4 Amphothericin B 2.4 Ethyl alcohol 76.2 C. LIQUID POLYMER COMPOSITION ROOT CANAL STERILIZATION Methacrylic acid copolymer type A 6.9 Chlorhexidine digluconate 22.9 (20% aqueous solution) Polyethylene g 400 11.5 Ethyl alcohol 58.7 D. LIQUID POLYMER COMPOSITION FOR APHTHO ULCERS AND FOOD (i.e. PIZZA) BURNS Methacrylic acid copolymer type A Sodium saccharin 0.1 Polyethylene glycol 400 2.2 Ethyl alcohol 58.7 Purified water 19.0 E. LIQUID POLYMER COMPOSITION FOR APHTHOUS ULCER Methacrylic acid copolymer type A 21.9 Cetylpyridinium chloride 11.0 Lysine hydrochloride 0.2 Sodium saccharin 0.1 Polyethylene glycol 40 Ethyl alcohol 43.6 Purified water 19.5 F. LIQUID POLYMER COMPOSITION WISDOM TOOTH EXTRACTION Methacrylic acid copolymer type B 15.1 Chlorhexidine digluconate 23.3 (20% aqueous solution) Glycine 0.1 Polyethylene glycol 400 2.2 Sodium saccharin 0.1 Ethyl alcohol 58.7 Purified water 0.5 _____

EXAMPLE 20

Sustained Release of Camphorated p-Chlorophenol For Root Canal Sterilization

Experimental Method--Basic Components

Camphor (BP)--Merck

Chlorophenol (AR)--Fluka

EUDRAGIT S (Methacrylic acid copolymer, type B)--Roehm Pharma

Ethyl cellulose N100 (NF)--Hercules

Ethanol (USP)--Bio Lab

Absorbent points--Dentsply

Methods

1. Preparation of Camphorated p-Chlorophenol (CPK)

6.5 g camphor and 3.5 g chlorophenol were mixed together in a mortar crushed with a pestle until all the solids were liquified.

2. CPK Liquid Polymer Preparation--General Description

The formulations were all prepared by the same general procedure des as follows: camphorated p-chlorophenol was dissolved in ethanol and EUDRAGIT S was added slowly while stirring until all the polymer dissolved. Additional components were added while stirring continuou

3. Release of p-chlorophenol

NOTE: Since p-chlorophenol is the active antibacterial agent in CPK, was chosen to be the release marker in this system.

The release of chlorophenol was measured from film, coated absorbent points, and coated paper tissues (Kimwipes brand).

A. Film

3 g of the formulation was poured onto a teflon plate. The film was generated after allowing the solvent to evaporate for 5 hours. The f was cut and accurately weighed.

B. Coated absorbent points

An absorbent point was placed in the liquid polymer solution for 2 s allowed to dry. The amount of coating added to the absorbent point w accurately weighed.

C. Coated paper tissues

A paper tissue was placed in the liquid polymer solution and allowed dry. It was then cut into pieces and accurately weighed.

The film, coated absorbent point and/or coated paper tissue were the placed in vials containing 5 ml phosphate buffer (0.02M, pH 6.8) and incubated at 37.degree. C. They were then transferred at specific ti intervals to other vials containing buffer solution. The concentrati p-chlorophenol released was determined by a UV spectrophotometer (UV 930, Kontron Instruments) at 223.2 nm against a standard calibration curve.

4. Microbiological Testing

Two absorbent points were placed in the liquid polymer solution for and allowed to dry. The amount of film absorbed by the absorbent poi was accurately weighed. The absorbent points were placed in vials containing 1 ml sterile phosphate buffer (0.02M, pH 6.8) each and incubated at 37.degree. C. They were then transferred after 0.5, 1, 24 and 48 hours to other vials containing buffer solution. 0.2 ml wa taken at each stage for determination of chlorophenol concentration HPLC against a standard calibration curve, and 0.8 ml was transferre the microbiology lab for bacteriological testing.

A. Materials and Methods

Bacterial strain--Streptococcus mutans 1895 was studied.

Growth conditions--The test organism was grown aerobically at 37.deg C. overnight in Brain Heart Infusion broth (BHI, Difco, Detroit, Mic and then diluted with BHI to contain approximately 10.sup.3 colony-f units (CFU) per ml.

Susceptibility test--The test was performed in test tubes, according the broth dilution method. The volume of 0.8 ml of each tested solut was added to 1 ml of BHI. One (1) ml of the inoculum was added to ea test tube. After 24 h of aerobic incubation at 37.degree. C. the opt density was measured against BHI at 540 nm, in a Klett instrument.

Results

1. The Effect of Polymer and Plasticizer on the Release Profile from and a Coated Absorbent Point

The release of p-chlorophenol from film matrices and absorbent point coated with CPK was tested with a variety of formulations (Table XIX film was formed from formulation RK25.1, and very soft films were fo from other formulations containing polyethylene glycol 400 (PEG 400) (RK25.2-4). In general the release profiles reveal a burst effect (e or moderate depending on the formulation) followed by very slow rele over an extended period of time.

The chlorophenol release from film cast from formulations RK25.2-4 i presented in FIG. 19. It shows that a formulation containing EUDRAGI (RK25.3) possesses better properties of longer release than formulat with ethyl cellulose.

FIG. 20 shows the release of formulations RK25.1-4 from coated absor points. As is shown, formulation RK25.1 containing 11.3% PEG 400 rel the chlorophenol rapidly and completely, as in the absence of polyme Formulation RK25.3, containing less PEG 400, releases chlorophenol a much slower rate than RK25.1, and similar to the film (FIG. 19) rele slower than RK25.2 and RK25.1 as well.

It should be noted that the recovery of the drug from ethyl cellulose-coated absorbent points was incomplete.

Formulations RK25.5 and RK25.6, which do not contain PEG 400, demons

very slow release profiles for CPK (FIGS. 21 and 22) although they parallel those of formulations containing PEG 400 and either ethyl cellulose or EUDRAGIT S.

Chlorophenol was released from films prepared from formulations cont only camphorated parachlorophenol and polymer (RK25.5) for a period weeks, however only 50% of the total amount of the drug was released Nevertheless, the in vitro release from absorbent points was much fa (FIG. 21). FIG. 21 shows that most of the drug was released within 6 hours. The effect of PEG 400 on the release profile was also demonst using the coated absorbent point, as also seen in FIG. 21.

TABLE XIX

Weight percent of components in formulations Exp. No. RK25.1 RK25.2 RK25.4 RK25.5 RK25.6

CPK 22.6 22.6 22.6 11.8 4.7 4.7 EUDRAGIT S 6.8 -- 11.3 -- 11.8 -- ET CELLULOSE -- 6.8 -- 5.9 -- 7.1 PEG 400 11.3 11.3 6.8 3.5 -- -- ETHAN 59.3 59.3 59.3 78.8 83.5 85.2

2. The effect of CaCl.sub.2, MgCl.sub.2, and Tween 80 on the Release Profile of p-Chlorophenol from Matrices containing Ethyl Cellulose o EUDRAGIT S.

The effect of the addition of CaCl.sub.2, MgCl.sub.2 and Tween 80 (T XX) on the in vitro release profile is shown in FIG. 22. Addition of components cause increase in the burst release in both EUDRAGIT S an ethyl cellulose-containing formulations (ethyl cellulose RK25.8 and compared to RK25.6, EUDRAGIT S RK25.7, 9 and 11 compared to RK25.5).

Formulations RK25.5 (without PEG 400), RK25.7 (with CaCl.sub.2), RK2 (with Tween 80), and RK25.11 (with MgCl.sub.2) were compared over a period of time (see FIG. 23). This comparison shows that only the formulation with no additive shows a prolonged release profile, wher other release profiles diminished to zero after 24 hours, with incom recovery.

TABLE XX

Weight percent of components in formulations Exp. No. RK25.7 RK25.8 RK25.10 RK25.11 RK25.12

CPK 4.7 4.7 4.7 4.7 4.7 4.7 EUDRAGIT S 11.8 -- 11.8 -- 11.8 -- ETHYL CELLULOSE -- 7.1 -- 7.1 -- 7.1 CaCl.sub.2 2.4 2.4 -- -- -- -- TWEEN -- 4.7 4.7 -- -- MgCl.sub.2 -- -- -- -- 2.4 2.4 ETHANOL 81.1 85.8 78 83.54 81.1 85.8

By adding increasing amount of CaCl.sub.2 to the formulations (Table the release patterns from the films were diminished (FIG. 24 a-b).

No significant change in the release kinetics from the paper tissue observed (FIG. 25).

TABLE XXI Weight percent of components in formulations Exp. No.: RK39.1 RK39.2 RK39.3 RK39.5 CPK 4.7 4.7 4.7 4.7 EUDRAGIT 11.8 11.8 11.8 CaCl.sub.2 0.2 1.2 2.4 -- ETHANOL 83.3 82.3 81.1 83.5

FIGS. 26a-b show that the release profiles from paper tissues are af by the ratio between camphorated parachlorophenol and the polymer. A ratio rises, the burst effect is higher, and the second phase of rel begins sooner. It should be emphasized that formulations RK25.5 and had the same composition in the dry film (Tables XIX and XXII) and t release kinetics were practically the same, even though the ethanol content and viscosity of the formulation was different.

TABLE XXII The effect of vari concentrations of camphorated parachlorophenol and EUDRAGIT S weight percent of components in formulations Exp. No.: RK33.2 RK33.3 RK33.6 CPK 22.5 9.2 4.6 EUDRAGIT S 2 23.0 23.0 ETHANOL 45.0 67.8 73.4

3. Detailed Analysis of the Release Profile and Antibacterial Effect RK33.2

The release rate of CPK from absorbent points coated with formulatio RK33.2 was compared to that of CPK liquid alone. The results are sho Table XXIII and FIG. 27. It can be seen that the total amount of CPK released was almost identical in both, with a substantial difference the length of the release time. For CPK alone the release time was a hour, whereas the CPK liquid polymer lasted for up to 48 hours.

TABLE XXIII

Controlled Release of Camphorated Parachlorophenol (CPK) from Absorb Points (AP) for Root Canal Sterilization. CPK loading 1 hr release 6 release 22 hr release 48 hr release on AP (mg) (.mu.g/AP) (.mu.g/AP) (.mu.g/AP) (.mu.g/AP)

CPK 3.0 3016.0 3130.0 3130.0 3130.0 CPK-polymer 3.8 922.5 2154.2 277 3078.2 coating system (RK33.2)

Formulation RK33.2 was transferred to the pilot plant for 2.5 Kg production. The in vitro release of the product (CM-103) is presente FIG. 28. Table XXIV demonstrates that EUDRAGIT S is practically a non-degradable polymer. EUDRAGIT S is non-soluble in a buffer soluti pH 6.8. It is concluded, therefore, that the film formed would not d in the root canal.

TABLE XXIV Weight in mg CPK-polymer matrix 64 Polymer matrix after 34 14 day release CPK released in 14 days 28.7 (89.6%) Polymer lost 1.3

The bacterial growth inhibition by the absorbent points coated with formulation was studied. FIG. 29 shows results which were achieved f

formulation RK33.2 (CPK-polymer 1:1). The release kinetics profile o and RK33.2 from the absorbent points (FIG. 29) indicate that while t release from CPK-loaded absorbent points is completed within 3 hours sustained release for 48 hours is achieved when using formulation RK

Summary of the Root Canal Studies

Camphorated parachlorophenol was formulated with two types of polyme ethyl cellulose and EUDRAGIT S. These two polymers were chosen becau they are hydrophobic in nature and not easily degradable by body flu EUDRAGIT S has been definitely found to be the better polymer in ter controlling the CPK release for longer periods of time.

The figures and data show that:

1. The release kinetics include a short burst followed by a lower ra prolonged release. This phenomenon is an advantageous property of formulation designated for antibacterial treatments.

2. The use of film-coated absorbent points (using a formulation cont EUDRAGIT S) is better than the use of plain CPK liquid sorbed in abs points.

3. The release of chlorophenol from coated absorbent points is significantly faster than from film alone.

4. Additives to the formulations significantly increase the burst ef and almost eliminate the sustained-release patterns. MgCl.sub.2 and 80 also increase the total amount of drug released. The additives ar soluble in the buffer solution, probably causing the formation of po the film that facilitate release.

5. Film or coated absorbent points containing the plasticizer PEG 40 enhance the release rate to a very large extent. It seems that CPK i plasticizer by itself and the addition of PEG 400 is unnecessary.

6. The ratio between the active material and the polymer changed the release kinetics. Formulations containing high concentrations of CPK release larger portions of the active material. However the kinetics much faster, the short burst is large, and the release is finished s The formulations containing 1:1 polymer to CPK have been found to ha optimal ratio both by in vitro release kinetics and by the microbiol study.

Therefore, in summary, the best formulation for absorbent points was to be RK33.2, which showed an antibacterial effect for at least 48 h in the in vitro studies. The amount of coated polymer that was lost in vitro studies did not exceed 3%, demonstrating the non-degradable feature of the coated absorbent point. The burst effect demonstrated this particular formulation was sufficient to eliminate the majority bacteria in the root canal. The prolonged CPK release assured a low of bacteria, and that no reinfection of the root canal could take pl

EXAMPLE 21

Use of RAA to Alter the Release Rates of Active Agents

In the following Table XXV, unless otherwise noted, amounts are in g

TABLE XXV Exp. No.: C-176 C-1
C-187 Tween 80 0.5 0.5 0.5 So
4.5 2.5 -- EUDRAGIT L 4.4 4.4 4.4 CHDG 20% 3 ml 3 ml 3 ml L-Arginine
2.0 2.0 Alcohol 95% 21 ml 21 ml 21 ml Sodium polyphosphate -- -- 2.5
Water, purified 9 ml 9 ml 9 ml

As shown in FIG. 30, when no arginine was added to the preparation, release occured very slowly with a maximum recovery of 20-30% even t the film eventually degraded. As arginine was incorporated, the rele was dramatically increased with almost complete recovery. Moreover, film was more hydrophilic than usual and its degradation was fitted to the term dissolution than to the other examples. However, the rat release can be further adjusted by using agents such as sodium polyphosphate at different concentrations.

Having now fully described the invention, it will be understood by t with skill in the art that the scope may be performed with a wide an equivalent range of conditions, parameters, and the like, without affecting the spirit or scope of the invention or any embodiment the

CLAIMS:

What is claimed is:

1. A sustained-released liquid polymer composition which consists essentially of:

(a) one or more sustained release acrylic polymers;

(b) a pharmacological agent;

(c) a release adjusting agent selected from the group consisting of cross-linking agent, a polysaccharide, a lipid, a protein, a sodium citrate, sodium docusate, an amino acid and sodium polyphosphate; an

(d) a pharmaceutically acceptable vehicle selected from the group consisting of water; ethyl alcohol; and ethyl alcohol and water,

wherein said sustained release acrylic polymers are selected from th group consisting of:

(1) a methacrylic acid type A copolymer, an anionic copolymer based methacrylic acid and methylmethacrylate wherein the ratio of free ca groups to the ester groups is approximately 1:1;

(2) a methacrylic acid type B compolymer, an anionic copolymer based methacrylic acid and methylmethacrylate wherein the ratio of free ca groups to the ester groups is approximately 1:2,

(3) a dimethylaminoethylacrylate/ethylmethacrylate copolymer, a copo based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium g to the remaining neutral (meth)acrylic acid esters is 1:20; and

(4) an ethyl methacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters low content of quaternary ammonium groups wherein the molar ratio of ammonium groups to the remaining neutral (meth)acrylic acid esters i 1:40.

2. The liquid polymer composition of claim 1, wherein said amino aci selected from the group consisting of: arginine, lysine, aspartic ac and glutaric acid.

3. The liquid polymer composition of claim 1, wherein said pharmacol agent is selected from the group consisting of: an antibiotic, an antiseptic, an anti-fungal agent, an anti-viral agent, and a hypersensitivity agent.

4. The liquid polymer composition of claim 1, wherein said pharmacol agent is a bacteriocidal quaternary ammonium salt.

5. The liquid polymer composition of claim 4 wherein said bacterioci quaternary ammonium salt is selected from the group consisting of cetylpyridinium chloride and benzalkonium chloride.

6. The liquid polymer composition of claim 5, wherein said bacterioc quaternary ammonium salt is cetylpyridinium chloride.

7. The liquid polymer composition of claim 5, wherein said bacterioc quaternary ammonium salt is benzalkonium chloride.

8. The liquid polymer composition of claim 3, wherein said pharmacol agent is a hypersensitivity agent.

9. The liquid polymer composition of claim 8, wherein said hypersensitivity agent is selected from the group consisting of a strontium salt, a potassium salt, a fluoride and an oxylate.

10. The liquid polymer composition of claim 9, wherein said strontiu is selected from the group consisting of strontium chloride and stro citrate.

11. The liquid polymer composition of claim 9, wherein said potassiu is selected from the group consisting of potassium chloride, potassi hydrogen tartrate and potassium nitrate.

12. The liquid polymer composition of claim 9, wherein said fluoride stannous fluoride.

13. The liquid polymer composition of claim 9, wherein said oxylate potassium hydrogen oxylate.

14. A sustained-released liquid polymer composition which consists essentially of:

(a) one or more sustained release acrylic polymers;

(b) a pharmacological agent;

(c) a release adjusting agent selected from the group consisting of

cross-linking agent, a polysaccharide, a lipid, a protein, a sodium citrate, sodium docusate, an amino acid and sodium polyphosphate;

(d) a pharmaceutically acceptable vehicle selected from the group consisting of water; ethyl alcohol; and ethyl alcohol and water; and

(e) a plasticizer;

wherein said sustained release acrylic polymers are selected from th group consisting of:

(1) a methacrylic acid type A copolymer, an anionic copolymer based methacrylic acid and methylmethacrylate wherein the ratio of free ca groups to the ester groups is approximately 1:1;

(2) a methacrylic acid type B copolymer, an anionic copolymer based methacrylic acid and methylmethacrylate wherein the ratio of free ca groups to the ester groups is approximately 1:2;

(3) a dimethylaminoethylacrylate/ethylmethacrylatecopolymer, a copol based on acrylic and methacrylic acid esters with a low content of quaternary ammonium groups wherein the molar ratio of the ammonium g to the remaining neutral (meth)acrylic acid esters is 1:20; and

(4) an ethyl methacrylate/chlorotrimethylammoniumethyl methacrylate copolymer, a copolymer based on acrylic and methacrylic acid esters low content of quaternary ammonium groups wherein the molar ratio of ammonium groups to the remaining neutral (meth)acrylic acid esters i 1:40.

15. The liquid polymer composition of claim 14, wherein said plastic is selected from the group consisting of: polyethylene glycol and di phthalate.

16. The liquid polymer composition of claim 1, wherein said cross-li agent is selected from the group consisting of glutaraldehyde, citri acid, lysine, aspartic acid, and glutaric acid.

17. The liquid polymer composition of claim 1, wherein said polysacc is dextran.

18. The liquid polymer composition of claim 1, wherein said lipid is sodium docusate.

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USPT,PGPB,JPAB,EPAB,DWPI	l1 and (nail adj varnish or nail adj polish or nail adj lacquer)	0	L2
USPT,PGPB,JPAB,EPAB,DWPI	(acyclovir or amantadine or cidofovir or famciclovir or foscarnet or ganciclovir or palivizumab or penciclovir or ribavirin or rimantadine or valcyclovir) and(cosmetic)	491	L1

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☐ 1. Document ID: US 20010003735 A1

L3: Entry 1 of 72 File: PGPB Jun 14, 2001

PGPUB-DOCUMENT-NUMBER: 20010003735
PGPUB-FILING-TYPE: new-utility
DOCUMENT-IDENTIFIER: US 20010003735 A1

TITLE: Thickened butyrolactone-based nail polish remover with applicator

PUBLICATION-DATE: June 14, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Perlman, Daniel	Arlington	MA	US	

US-CL-CURRENT: 510/118; 510/480, 510/506

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 6231875 B1

L3: Entry 2 of 72 File: USPT May 15, 2001

US-PAT-NO: 6231875
DOCUMENT-IDENTIFIER: US 6231875 B1

TITLE: Acidified composition for topical treatment of nail and skin conditions

DATE-ISSUED: May 15, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sun; Ying	Somerville	NJ	N/A	N/A
Liu; Jue-Chen	Neshanic	NJ	N/A	N/A
Kimbleton; Elizabeth	Princeton	NJ	N/A	N/A
Wang; Jonas C. T.	Robbinsville	NJ	N/A	N/A

US-CL-CURRENT: 424/401; 424/404, 424/61

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6224887 B1

L3: Entry 3 of 72 File: USPT May 1, 2001

US-PAT-NO: 6224887
DOCUMENT-IDENTIFIER: US 6224887 B1

TITLE: Antifungal nail lacquer and method using same

DATE-ISSUED: May 1, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Samour; Carlos M.	Bedford	MA	N/A	N/A
Krauser; Scott F.	Tyngsboro	MA	N/A	N/A

US-CL-CURRENT: 424/401; 424/404, 424/61

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 4. Document ID: US 6221900 B1

L3: Entry 4 of 72 File: USPT Apr 24, 2001

US-PAT-NO: 6221900
DOCUMENT-IDENTIFIER: US 6221900 B1

TITLE: BTK inhibitors and methods for their identification and use

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN	N/A	N/A
Zheng; Yaguo	New Brighton	MN	N/A	N/A
Ghosh; Sutapa	Shoreview	MN	N/A	N/A

US-CL-CURRENT: 514/457; 514/312, 514/432, 546/156, 546/157, 549/23, 549/399, 549/404, 549/405, 549/407

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 5. Document ID: US 6214994 B1

L3: Entry 5 of 72 File: USPT Apr 10, 2001

US-PAT-NO: 6214994
DOCUMENT-IDENTIFIER: US 6214994 B1

TITLE: Certain substituted 1-aryl-3-piperazin-1'-yl propanones

DATE-ISSUED: April 10, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
DeBernardis; John Francis	Lindenhurst	IL	N/A	N/A
Kerkman; Daniel Joseph	Lake Villa	IL	N/A	N/A
Zinkowski; Raymond Paul	Northbrook	IL	N/A	N/A

US-CL-CURRENT: 544/376; 544/391, 544/399

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 6191167 B1

L3: Entry 6 of 72 File: USPT Feb 20, 2001

US-PAT-NO: 6191167
DOCUMENT-IDENTIFIER: US 6191167 B1

TITLE: Pharmaceutical compositions containing hydroxycarboxylic acid and/or ketocarboxylic acids and methods of using the same

DATE-ISSUED: February 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Ruey J.	Ambler	PA	N/A	N/A
Van Scott; Eugene J.	Abington	PA	N/A	N/A

US-CL-CURRENT: 514/558; 424/401, 424/642, 424/691, 514/114, 514/12, 514/19, 514/2, 514/23, 514/349, 514/399, 514/419, 514/518, 514/532, 514/547, 514/561, 514/562, 514/567

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 6187761 B1

L3: Entry 7 of 72 File: USPT Feb 13, 2001

US-PAT-NO: 6187761
DOCUMENT-IDENTIFIER: US 6187761 B1

TITLE: Production and use of compositions comprising high concentrations of vitamin B12 activity

DATE-ISSUED: February 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bijl; Hendrik Louis	Vlaardingen	N/A	N/A	NLX

US-CL-CURRENT: 514/52; 435/170, 435/86, 536/26.4, 536/26.41, 536/26.42

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 6180379 B1

L3: Entry 8 of 72 File: USPT Jan 30, 2001

US-PAT-NO: 6180379
DOCUMENT-IDENTIFIER: US 6180379 B1

TITLE: Cyclin-selective ubiquitin carrier polypeptides

DATE-ISSUED: January 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ruderman; Joan V.	Wellesley	MA	N/A	N/A
Hershko; Avram	Haifa	N/A	N/A	ILX
Kirschner; Marc W.	Newton	MA	N/A	N/A
Townsley; Fiona	Somerville	MA	N/A	N/A
Aristarkov; Alexander	Boston	MA	N/A	N/A
Eytan; Esther	Haifa	N/A	N/A	ILX
Yu; Hongtao	Somerville	MA	N/A	N/A

US-CL-CURRENT: 435/193; 435/68.1, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 9. Document ID: US 6160010 A

L3: Entry 9 of 72 File: USPT Dec 12, 2000

US-PAT-NO: 6160010
DOCUMENT-IDENTIFIER: US 6160010 A

TITLE: BTK inhibitors and methods for their identification and use

DATE-ISSUED: December 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN	N/A	N/A
Zheng; Yaguo	New Brighton	MN	N/A	N/A
Ghosh; Sutapa	Shoreview	MN	N/A	N/A

US-CL-CURRENT: 514/521; 514/238.5, 514/331, 514/428, 514/548, 544/163, 546/230, 548/567, 558/392, 560/250

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 10. Document ID: US 6156711 A

L3: Entry 10 of 72 File: USPT Dec 5, 2000

US-PAT-NO: 6156711
DOCUMENT-IDENTIFIER: US 6156711 A

TITLE: Thickened butyrolactone-based nail polish remover with applicator

DATE-ISSUED: December 5, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Perlman; Daniel	Arlington	MA	N/A	N/A

US-CL-CURRENT: 510/118; 510/505

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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USPT,PGPB,JPAB,EPAB,DWPI	l2 and (solvent(2a)non adj volatile)	72	L3
USPT,PGPB,JPAB,EPAB,DWPI	l1 and (antifungal)	83	L2
USPT,PGPB,JPAB,EPAB,DWPI	(methacrylic adj acid(3a)copolymer adj type B or type C or type A) and (nail adj polish or nail adj lacquer or nail adj varnish)	2708	L1

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Search Results - Record(s) 11 through 20 of 72 returned.

☐ 11. Document ID: US 6143794 A

L3: Entry 11 of 72 File: USPT Nov 7, 2000

US-PAT-NO: 6143794
DOCUMENT-IDENTIFIER: US 6143794 A

TITLE: Topical formulations for the treatment of nail fungal diseases

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chaudhuri; Bhaskar	Cupertino	CA	N/A	N/A
Chim; Ming Fai	San Francisco	CA	N/A	N/A
Bucks; Daniel	Millbrae	CA	N/A	N/A

US-CL-CURRENT: 514/655

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

☐ 12. Document ID: US 6143793 A

L3: Entry 12 of 72 File: USPT Nov 7, 2000

US-PAT-NO: 6143793
DOCUMENT-IDENTIFIER: US 6143793 A

TITLE: Use of hydrophilic penetration agents in dermatological compositions for the treatment of onychomycoses, and corresponding compositions

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Laugier; Jean-Pierre	Antony	N/A	N/A	FRX
Rude; Marie-France	Villejuif	N/A	N/A	FRX
Touzan; Philippe	Ramonville Saint Agne	N/A	N/A	FRX
Rigenbach; Francois	Bagneux	N/A	N/A	FRX

US-CL-CURRENT: 514/655; 514/724

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 13. Document ID: US 6075026 A

L3: Entry 13 of 72 File: USPT Jun 13, 2000

US-PAT-NO: 6075026
DOCUMENT-IDENTIFIER: US 6075026 A

TITLE: Certain substituted 1-aryl-3-piperazin-1'-yl propanones

DATE-ISSUED: June 13, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
DeBernardis; John Francis	Lindenhurst	IL	N/A	N/A
Kerkman; Daniel Joseph	Lake Villa	IL	N/A	N/A
Zinkowski; Raymond Paul	Northbrook	IL	N/A	N/A

US-CL-CURRENT: 514/252.12; 514/231.5, 514/231.8, 514/252.13, 514/253.01, 514/253.12, 514/254.11, 514/255.01, 514/322, 514/324, 514/326, 514/364, 514/378, 544/367, 548/248

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 14. Document ID: US 6060512 A

L3: Entry 14 of 72 File: USPT May 9, 2000

US-PAT-NO: 6060512
DOCUMENT-IDENTIFIER: US 6060512 A

TITLE: Method of using hydroxycarboxylic acids or related compounds for treating skin changes asociated with intrinsic and extrinsic aging

DATE-ISSUED: May 9, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Ruey J.	Ambler	PA	N/A	N/A
Van Scott; Eugene J.	Abington	PA	N/A	N/A

US-CL-CURRENT: 514/558; 514/114, 514/12, 514/19, 514/2, 514/23, 514/349, 514/399, 514/419, 514/518, 514/532, 514/547, 514/557, 514/561, 514/562, 514/567, 514/844, 514/941

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 15. Document ID: US 5993790 A

L3: Entry 15 of 72 File: USPT Nov 30, 1999

US-PAT-NO: 5993790
DOCUMENT-IDENTIFIER: US 5993790 A

TITLE: Nail evulsion compositions and method for evulsing nails and treating nail and nail bed infections

DATE-ISSUED: November 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Strauss; Richard	Woodbury	NY	N/A	N/A

US-CL-CURRENT: 424/61; 424/401, 424/487, 424/78.02, 424/78.07, 514/858

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 16. Document ID: US 5955321 A

L3: Entry 16 of 72 File: USPT Sep 21, 1999

US-PAT-NO: 5955321
DOCUMENT-IDENTIFIER: US 5955321 A

TITLE: Production and use of compositions comprising high concentrations of vitamin B12 activity

DATE-ISSUED: September 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bijl; Hendrik Louis	Vlaardingen	N/A	N/A	NLX

US-CL-CURRENT: 435/86; 435/170, 435/822, 514/52, 536/26.4, 536/26.41, 536/26.42

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Drawi Desc | Image

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☐ 17. Document ID: US 5916545 A

L3: Entry 17 of 72 File: USPT Jun 29, 1999

US-PAT-NO: 5916545
DOCUMENT-IDENTIFIER: US 5916545 A

TITLE: Antifungal nail solution

DATE-ISSUED: June 29, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Burnett; Debbie L.	Basking Ridge	NJ	N/A	N/A
DeVincentis; Teresa J.	Flanders	NJ	N/A	N/A
Dubash; Darius D.	Pine Brook	NJ	N/A	N/A
Ladas; Athanasios S.	Parsippany	NJ	N/A	N/A

US-CL-CURRENT: 424/61; 514/397, 514/777

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Drawi Desc | Image

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☐ 18. Document ID: US 5885552 A

L3: Entry 18 of 72 File: USPT Mar 23, 1999

US-PAT-NO: 5885552
DOCUMENT-IDENTIFIER: US 5885552 A

TITLE: Mouthrinse

DATE-ISSUED: March 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Causton; Brian Edward	Aldermaston	N/A	N/A	GBX

US-CL-CURRENT: 424/49; 424/435, 424/48

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 19. Document ID: US 5886042 A

L3: Entry 19 of 72 File: USPT Mar 23, 1999

US-PAT-NO: 5886042
DOCUMENT-IDENTIFIER: US 5886042 A

TITLE: Amphoteric compostion and polymeric forms of alpha hydroxyacids, and their therapeutic use

DATE-ISSUED: March 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Ruey J.	Ambler	PA	N/A	N/A
Van Scott; Eugene J.	Abington	PA	N/A	N/A

US-CL-CURRENT: 514/557; 424/401, 514/114, 514/19, 514/2, 514/23, 514/532, 514/558, 514/844, 514/941

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 20. Document ID: US 5886041 A

L3: Entry 20 of 72 File: USPT Mar 23, 1999

US-PAT-NO: 5886041
DOCUMENT-IDENTIFIER: US 5886041 A

TITLE: Amphoteric compositions and polymeric forms of alpha hydroxyacids, and their therapeutic use

DATE-ISSUED: March 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Ruey J.	Ambler	PA	N/A	N/A
Van Scott; Eugene J.	Abington	PA	N/A	N/A

US-CL-CURRENT: 514/557; 424/401, 514/114, 514/19, 514/2, 514/23, 514/532, 514/558, 514/844, 514/941

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Terms	Documents
l2 and (solvent(2a)non adj volatile)	72

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